

# PRV

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## FIELD OF THE INVENTION

The present invention relates to new compounds, to pharmaceutical formulations  
5 containing said compounds and to the use of said compounds in therapy. The present  
invention further relates to processes for the preparation of said compounds and to the use  
of intermediates in the preparation thereof.

## 10 BACKGROUND OF THE INVENTION

Pain sensation in mammals is due to the activation of the peripheral terminals of a  
specialized population of sensory neurons known as nociceptors. Capsaicin, the active  
ingredient in hot peppers, produces sustained activation of nociceptors and also produces a  
15 dose-dependent pain sensation in humans. Cloning of the vanilloid receptor 1 (VR1 or  
TRPV1) demonstrated that VR1 is the molecular target for capsaicin and its analogues:  
(Caterina, M.J., Schumacher, M.A., et al. Nature 1997 v.389 p 816-824). Functional studies  
using VR1 indicate that it is also activated by noxious heat and that the threshold for  
activation can be lowered below normal body temperature by a reduction of the  
20 extracellular pH value (acidification) and by other inflammatory mediators Tominaga, M.,  
Caterina, M.J. et al. Neuron 1998 v.21, p.531-543). Expression of VR1 is also regulated  
after peripheral nerve damage of the type that leads to neuropathic pain. These properties  
of VR1 make it a highly relevant target for pain and for diseases involving inflammation.  
Agonists of the VR1 receptor can act as analgesics, but the usefulness of agonists, such as  
25 capsaicin and its analogues, is limited by their pungency, neurotoxicity and induction of  
hypothermia. Pain-evoking stimuli activate the VR1 receptor and agents that block the  
activity of VR1 have also shown analgesic activity in animals.

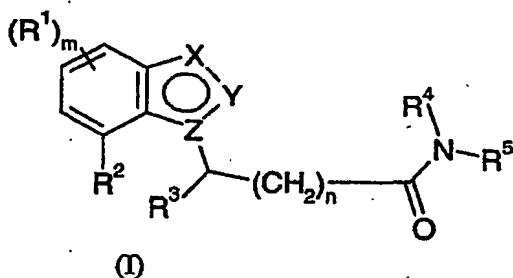
Compounds with VR1 blocker activity are believed to be of potential use for the treatment  
or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic  
30 origin such as arthritis, fibromyalgia, low back pain and post-operative pain. (Walker et al  
J Pharmacol Exp Ther. 2003 Jan; 304(1):56-62), or visceral pains such as chronic pelvic  
pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, and also

neuropathic pain such as sciatica, diabetic neuropathy and HIV neuropathy, and the like (Walker et al *ibid*, Rashid et al J Pharmacol Exp Ther. 2003 Mar;304(3):940-8). These compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang and Oh Curr Opin Pharmacol 2002 Jun; 2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int 2001 Jun; 87(9): 774-9, Szallasi Am J Clin Pathol 2002 118: 110-21). VR1 inhibitors are also of potential use for the treatment or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi *ibid*).

#### DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an activity at the vanilloid receptor 1 (VR1).

The present invention provides a compound of formula I



wherein:

$R^1$  is H,  $\text{NO}_2$ ,  $\text{NH}_2$ , halo,  $\text{NR}^6\text{R}^7$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{C}_{1-6}\text{haloalkyl}$ ,  $\text{C}_{1-6}\text{haloalkylO}$ ,  $\text{C}_{1-6}\text{alkylOC}_{0-6}\text{alkyl}$ ,  $\text{R}^6\text{OC}_{1-6}\text{alkyl}$ ,  $\text{R}^6\text{CO}$ ,  $\text{CO}_2\text{R}^6$  or  $\text{CONR}^6\text{R}^7$ ;

$m$  is 0, 1, 2, 3 or 4;

$R^2$  is H,  $\text{NO}_2$ ,  $\text{NH}_2$ , halo,  $\text{NR}^6\text{R}^7$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{C}_{1-6}\text{haloalkyl}$ ,

C<sub>1-6</sub>haloalkylO, C<sub>0-6</sub>alkylcyano, C<sub>1-6</sub>alkylOC<sub>0-6</sub>alkyl, R<sup>6</sup>OC<sub>1-6</sub>alkyl, R<sup>6</sup>CO, CO<sub>2</sub>R<sup>6</sup> or CONR<sup>6</sup>R<sup>7</sup>, R<sup>8</sup>SO<sub>2</sub>, arylC<sub>0-6</sub>alkyl, heteroarylC<sub>0-6</sub>alkyl, NR<sup>6</sup>R<sup>7</sup>, NCOR<sup>6</sup>, NHCOR<sup>6</sup> or NHSO<sub>2</sub>R<sup>6</sup>;

X, Y and Z are each independently C, CR<sup>6</sup>, N or NR<sup>6</sup>;

5 R<sup>3</sup> is H or C<sub>0-4</sub>alkyl;

n is 0, 1, 2, 3 or 4;

R<sup>4</sup> is H or C<sub>0-4</sub>alkyl;

R<sup>5</sup> is H, C<sub>1-10</sub>alkyl, C<sub>5-6</sub>aryl, C<sub>3-7</sub>cycloalkyl, C<sub>5-6</sub>heteroaryl, whereby any aryl or cycloalkyl may be fused with heteroaryl, C<sub>3-7</sub>cycloalkyl or C<sub>3-7</sub>heterocycloalkyl;

10 and R<sup>4</sup> and R<sup>5</sup> may be substituted with one or more A; and

A is H, OH, NO<sub>2</sub>, NH<sub>2</sub>, CO, O(CO), halo, C<sub>1-6</sub>alkyl, NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>alkylOC<sub>0-6</sub>alkyl, R<sup>6</sup>OC<sub>1-6</sub>alkyl, R<sup>6</sup>CO, CO<sub>2</sub>R<sup>6</sup> or CONR<sup>6</sup>R<sup>7</sup>;

R<sup>6</sup> and R<sup>7</sup> are each independently H or C<sub>1-6</sub>alkyl;

R<sup>8</sup> is NR<sub>6</sub>R<sub>7</sub> or C<sub>0-4</sub>alkyl

15 or salts, solvates or solvated salts thereof,

with the proviso the compound is not 2-Indol-1-yl-N-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide.

A further embodiment of the invention relates to compounds selected from the group  
20 consisting of

N-(3-Fluoro-4-methoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

N-(2-Fluoro-4-trifluoromethylphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

N-(3-Chloro-4-iodo-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

N-(3-Chloro-4-methoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

25 N-(3-Difluoromethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

N-(3-Methoxy-5-trifluoromethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

N-(3,5-Difluoro-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethoxy-phenyl)-acetamide,

N-(3-Methoxy-5-trifluoromethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

30 2-(7-Nitro-1H-benzoimidazol-1-yl)-N-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-acetamide,

N-(4-tert-Butyl-phenyl)-2-(7-nitrobenzoimidazol-1-yl)-acetamide,

N-[3-(1-Hydroxy-ethyl)-phenyl]-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethyl-phenyl)-acetamide,  
N-(3-Chloro-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-Hexyl-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,4-Difluoro-phenyl)-2-(7-nitrobenzoimidazol-1-yl)-acetamide,  
5 N-(4-Cyano-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(2-Bromo-benzyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethyl-benzyl)-acetamid,  
N-(4-Methyl-pyridin-2-yl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
10 N-(3-Cyano-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,5-Dimethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Methoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Ethoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,4-Dimethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
15 2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3,4,5-trimethoxy-phenyl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethoxyphenyl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-phenoxy-phenyl)-acetamide,  
N-(4-Butyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(2-Fluoro-4-iodo-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
20 2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(2-trifluoromethyl-benzyl)-acetamide,  
N-(4-Methoxyphenyl)-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[2-(trifluoromethoxy)phenyl]acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-(2-phenoxyphenyl)acetamide,  
N-(4-Bromo-2-fluorophenyl)-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
25 N-[3-(Methylsulfonyl)phenyl]-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
N-[4-(Methylsulfonyl)phenyl]-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[2-(trifluoromethoxy)phenyl]acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)benzyl]acetamide,  
N-(4-tert-Butyl-benzyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
30 N-Indan-5-yl-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethoxy-benzyl)-acetamide,  
N-(4-Isopropyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

- N-(3,4-Dimethyl-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-Benzo[1,3]dioxol-5-yl-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-(3-Bromo-4-trifluoromethoxy-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-(3-Fluoro-2-methoxy-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
5 N-(3,5-Dimethoxyphenyl)-2-(7-nitro-1H-benzimidazol-1-yl)propanamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-(3-ethoxyphenyl)propanamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]propanamide,  
2-(7-Bromo-1H-benzimidazol-1-yl)-N-(3,5-dimethoxyphenyl)acetamide,  
2-(7-bromo-1H-benzimidazol-1-yl)-N-(3-methoxyphenyl)acetamide,  
10 2-(7-bromo-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide,  
2-(7-Chloro-1H-benzimidazol-1-yl)-N-(3,5-dimethoxy-phenyl)-acetamide,  
2-(7-Chloro-1H-benzimidazol-1-yl)-N-(3-trifluoromethyl-phenyl)-acetamide,  
2-(7-Chloro-1H-benzimidazol-1-yl)-N-p-tolyl-acetamide,  
2-(7-Methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)acetamide,  
15 N-(3,5-Dimethoxyphenyl)-2-(7-methyl-1H-benzimidazol-1-yl)acetamide,  
2-(7-Methyl-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide,  
3-[(3,4-Dimethyl-phenylcarbamoyl)-methyl]-3H-benzimidazole-4-carboxylic acid methyl  
ester,  
3-(Indan-5-ylcarbamoylmethyl)-3H-benzimidazole-4-carboxylic acid methyl ester,  
20 3-[(4-tert-Butyl-benzylcarbamoyl)-methyl]-3H-benzimidazole-4-carboxylic acid methyl  
ester,  
3-[(3-Methoxy-5-trifluoromethyl-phenylcarbamoyl)-methyl]-3H-benzimidazole-4-  
carboxylic acid methyl ester,  
3-[(3,5-Dimethoxy-phenylcarbamoyl)-methyl]-3H-benzimidazole-4-carboxylic acid  
25 methyl ester,  
N-(3,5-Dimethoxyphenyl)-2-{7-[(dimethylamino)sulfonyl]-1H-benzimidazol-1-  
yl}acetamide,  
2-{7-[(Dimethylamino)sulfonyl]-1H-benzimidazol-1-yl}-N-[3-  
(trifluoromethyl)phenyl]acetamide,  
30 N-(3,5-Dimethoxyphenyl)-2-[7-(propylsulfonyl)-1H-benzimidazol-1-yl]acetamide,  
2-[7-(Propylsulfonyl)-1H-benzimidazol-1-yl]-N-[3-(trifluoromethyl)phenyl]acetamide and  
N-(3,5-Dimethoxyphenyl)-2-[7-(trifluoromethyl)-1H-benzimidazol-1-yl]acetamide,

or salts, solvates or solvated salts thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

5 For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

10 For the avoidance of doubt it is to be understood that in this specification 'C<sub>1-6</sub>' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

15 In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C<sub>1-3</sub> alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl, i-propyl or *tert*-butyl.

20 The term 'C<sub>0</sub>' means a bond or does not exist. For example when R<sup>3</sup> is C<sub>0</sub>alkyl, R<sup>3</sup> is a bond and "arylC<sub>0</sub>alkyl" is equivalent with "aryl", "C<sub>2</sub>alkylOC<sub>0</sub>alkyl" is equivalent with "C<sub>2</sub>alkylO".

25 In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C<sub>2-6</sub>alkenyl" having 2 to 6 carbon atoms and one or two double bonds, may be, but is not limited to vinyl, allyl, propenyl, butenyl, crotyl, pentenyl, or hexenyl, and a butenyl group may for example be buten-2-yl, buten-3-yl or buten-4-yl.

30 In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C<sub>2-6</sub>alkynyl" having 2 to 6 carbon atoms and

one or two trippel bonds, may be, but is not limited to etynyl, propargyl, pentynyl or hexynyl and a butynyl group may for example be butyn-3-yl or butyn-4-yl.

5 In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term " $C_{3-7}$ cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocycloalkyl" denotes a 3- to 7-membered, non-aromatic, partially or completely saturated hydrocarbon group, which contains one rings and at least one  
10 heteroatom. Examples of said heterocycle include, but are not limited to pyrrolidiny, pyrrolidonyl, piperidiny, piperaziny, morpholiny, oxazolyl, 2-oxazolidonyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term "aryl" refer to an optionally  
15 substituted monocyclic or bicyclic hydrocarbon unsaturated aromatic ring system. Examples of "aryl" may be, but are not limited to phenyl and naphthyl.

In this specification, unless stated otherwise, the term "heteroaryl" refer to an optionally substituted monocyclic or bicyclic unsaturated aromatic ring system containing at least one  
20 heteroatom selected independently form N, O or S. Examples of "heteroaryl" may be, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridaziny, pyrimidiny, pyraziny, tetrazolyl, triazolyl and oxazolyl.

25 In this specification, unless stated otherwise, the term "arylalkyl" and "heteroarylalkyl" refer to a substituent that is attached via the alkyl group to an aryl or heteroaryl group.

In this specification, unless stated otherwise, the term "halo" and "halogen" may be fluoro, iodo, chloro or bromo.

30 In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term " $C_{1-6}$ haloalkyl"



may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C<sub>1-6</sub>haloalkylO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

5

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

10

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

15

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18<sup>th</sup> Edition, Mack Publishing Co.).

20

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of formula I.

#### Methods of Preparation

25

Another aspect of the present invention provides processes for preparing compounds of formula I, or salts, solvates or solvated salts thereof.

30

Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in

"Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4<sup>th</sup> ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). For representative examples of heterocyclic chemistry see for example "Heterocyclic Chemistry", J. A. Joule, K. Mills, G. F. Smith, 3<sup>rd</sup> ed. Chapman and Hall (1995), p. 189-224 and "Heterocyclic Chemistry", T. L. Gilchrist, 2<sup>nd</sup> ed. Longman Scientific and Technical (1992), p. 248-282.

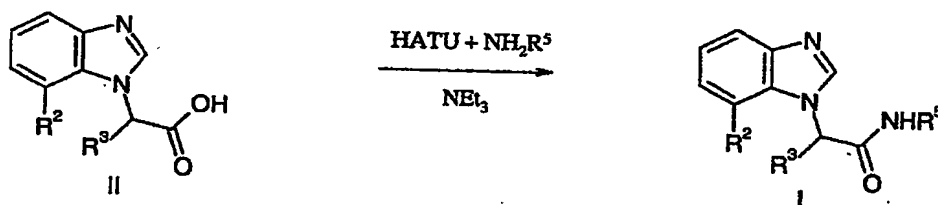
The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

One embodiment of the invention relates to processes for the preparation of the compound of formula I according to Methods A and B, wherein R<sup>1</sup> to R<sup>4</sup>, unless otherwise specified, are defined as in formula I, comprising;

Another object of the invention are processes for the preparation of the compound of formula I wherein R<sup>1</sup> to R<sup>5</sup>, unless otherwise specified, are defined as in formula I, comprising;

#### Methods of Preparation

##### Method A



whereby the target compound of formula I is obtained from the acid of formula II or its deprotonated form, *via* its conversion into an activated form, i.e. either the acyl chloride by treatment with oxalyl chloride or the mixed anhydride by treatment with *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and further treatment with an appropriate amine NH<sub>2</sub>R<sup>5</sup>. This reaction may be performed in any manner known to the skilled man in the art. The activation may be performed using any

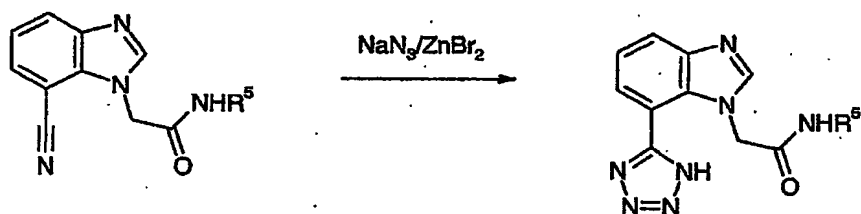
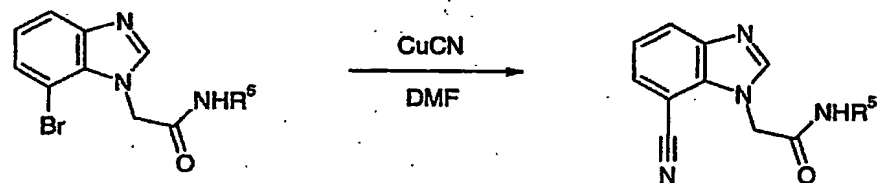
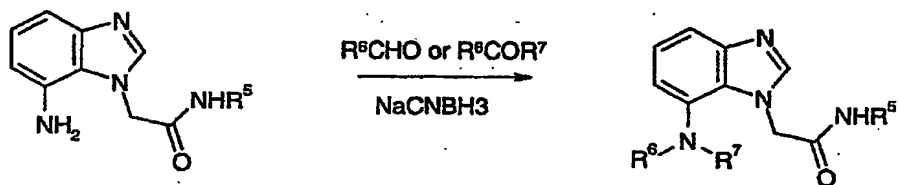
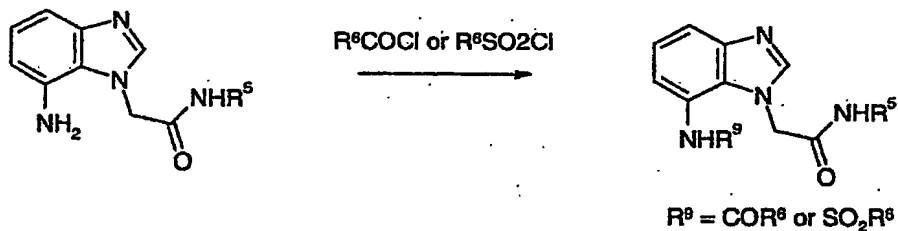
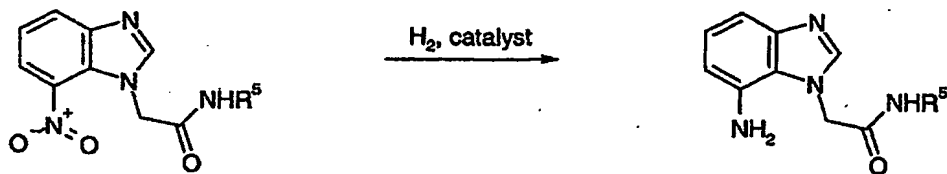
other similar activating reagent like 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride or 1,1'-carbonyldiimidazole. Suitable solvents to be used for this reaction may be halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or aprotic polar solvents like acetonitrile and dimethylformamide, or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between -30 and 50°C and the reaction time between 1 and 30 h.

Starting materials, the acids of formula II, may be obtained using multistep procedures described in detail in the following examples of synthesis starting from commercially available appropriately 1,2,3-trisubstituted benzenes.

Or,

15 Method B

whereby the target compound of formula I is obtained from an another compound of formula I by a chemical modification of the R<sup>2</sup> substituent using standard methods described in the literature, for example:



A further embodiment of the invention relates to compounds

2-bromo-*N*-(3-trifluoromethyl-phenyl)-propionamide,

benzimidazol-1-yl-acetic acid *tert*-butyl ester,

3-carboxymethyl-3*H*-benzimidazol-1-ium trifluoro-acetate,

2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide,

Synthesis of 4-methyl-1*H*-benzoimidazole,

2-Bromo-*N*-(3-dimethylamino-phenyl)-acetamide,

methyl 3-(1*H*-benzoimidazol-1-yl)propanoate ,

5 3-(1*H*-benzoimidazol-1-yl)propanoic acid,

methyl 4-(1*H*-benzoimidazol-1-yl)butanoate, and

4-(1*H*-benzoimidazol-1-yl)butanoic acid,

which may be used as intermediates in the preparation of compounds suited for the

treatment of VR1 mediated disorders, especially for use as intermediates for the

10 preparation of compounds of formula I.

#### Pharmaceutical formulation

According to one aspect of the present invention there is provided a pharmaceutical  
15 formulation comprising as active ingredient a therapeutically effective amount of the  
compound of formula I, or salts, solvates or solvated salts thereof, in association with one  
or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet,  
20 pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous,  
subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or  
emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal  
administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or  
25 more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

Suitable daily doses of the compound of formula I in the treatment of a mammal, including  
man are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about  
0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the  
active ingredients varies within a wide range and will depend on various factors such as the  
30 relevant indication, severity of the illness being treated, the route of administration, the  
age, weight and sex of the patient and the particular compound being used, and may be  
determined by a physician.

### Medical use

Surprisingly, it has been found that the compounds according to the present invention are  
5 useful in therapy. The compounds of formula I, or salts, solvates or solvated salts thereof,  
as well as their corresponding active metabolites, exhibit a high degree of potency and  
selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds  
of the present invention are expected to be useful in the treatment of conditions associated  
with excitatory activation of vanilloid receptor 1 (VR1).

10 The compounds may be used to produce an inhibitory effect of VR1 in mammals,  
including man.

VR1 are highly expressed in the peripheral nervous system and in other tissues.

Thus, it is expected that the compounds of the invention are well suited for the  
treatment of VR1 mediated disorders. The compounds of formula I are expected to  
15 be suited for the treatment of acute and chronic pain and acute and chronic  
inflammatory pain. The compound may further be suited for the treatment of chronic  
neuropathic pain.

Examples of such disorder may be selected from the group comprising of arthritis,  
fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain,  
20 cystitis, irritable bowel syndrome (IBS), pancreatitis, sciatica, diabetic neuropathy, HIV  
neuropathy, asthma, cough, inflammatory bowel disease (IBD) and psoriasis.

Further relevant disorders that may be treated using the compounds of formula I may be  
selected from the group comprising of gastro-esophageal reflux disease (GERD), emesis,  
urinary incontinence and hyperactive bladder.

25 The compounds of formula I may also be used as antitoxin to treat (over-) exposure  
to VR1 activators like capsaicin or tear gas, acids or heat.

The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the use of the compound of formula I in  
30 therapy.

Another embodiment of the invention relates to the use of the compound of formula I for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the use of the compound of formula I for  
5 treatment of acute and chronic pain disorders

Yet another embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic inflammatory pain.

10 Yet a further embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, for treatment of indications selected from the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatica, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary  
15 incontinence and hyperactive bladder.

One embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and  
20 chronic inflammatory pain and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above, comprising administering to a mammal,  
25 including man in need of such treatment, a therapeutically effective amount of the compound of formula I, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical formulation comprising the compound of formula I, as hereinbefore defined, for use in the treatment of VR1  
30 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

One embodiment of the invention relates to the use of 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above, comprising administering to a mammal, including man in need of such treatment, a therapeutically effective amount of 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide or 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide.

A further embodiment of the invention relates to a pharmaceutical formulation comprising 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide or 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide, for use in the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat", "therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "antagonist" and "inhibitor" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.



### Non- Medical use

In addition to their use in therapeutic medicine, the compounds of formula I, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

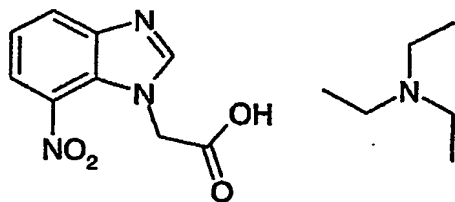
### Examples

The invention will now be illustrated by the following non-limiting examples.

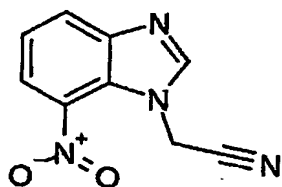
### General methods

All starting materials are commercially available or described in the literature. The  $^1\text{H}$  NMR spectra were recorded on Bruker at 400 MHz. The mass spectra were recorded utilising electrospray (LC-MS; LC: Waters 2790, column XTerra MS  $\text{C}_8$  2.5  $\mu\text{m}$  2.1X30 mm, buffer gradient  $\text{H}_2\text{O}+0.1\%\text{TFA}:\text{CH}_3\text{CN}+0.04\%\text{TFA}$ , MS: micromass ZMD// ammonium acetate buffer) ionisation techniques.

Synthesis of the key intermediates: 7- substituted benzoimidazol-1-yl-acetic acids



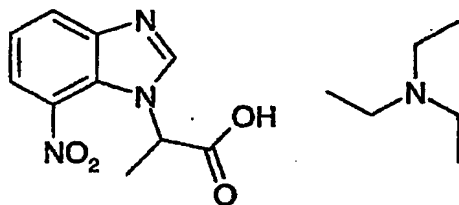
(7-Nitro-1H-benzoimidazol-1-yl)acetic acid triethylammonium salt



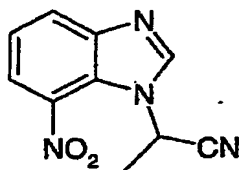
A. (7-Nitro-1*H*-benzoimidazol-1-yl)acetonitrile

A solution (1 M) of potassium *tert*-butoxide (16.1 mL) ) was slowly added to a solution of  
5 4(7)-nitro-1*H*-benzoimidazole (2.50 g, 15.3 mmol) in dry DMF (100 mL) at 0-5°C and the  
resulting dark-red solution was stirred for 15 min at room temperature. Bromoacetonitrile  
(1.12 mL, 16.1 mmol) was added in one portion and the reaction mixture was stirred for an  
additional hour, then quenched with dry ice and poured into 400 mL of cold water. The  
resulting clear solution was repeatedly extracted with CHCl<sub>3</sub> (4 × 80 mL). Organic extracts  
10 were pooled and washed with water (3 × 50 mL) and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and  
concentrated, yielding a 1:1 mixture of (4-nitro-1*H*-benzoimidazol-1-yl)acetonitrile and (7-  
nitro-1*H*-benzoimidazol-1-yl)acetonitrile. The regioisomers were separated on preparative  
HPLC (XTerra C<sub>8</sub> column 19×300 mm, 0.1 M aqueous NH<sub>4</sub>Ac/CH<sub>3</sub>CN). to yield (7-nitro-  
1*H*-benzoimidazol-1-yl)acetonitrile, 1.15 g (37%). MS (ESI) *m/z*: 203.05 [M+H].  
15 <sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) □ ppm 5.68 (s, 2 H) 7.50 (t, *J*=7.8 Hz, 1 H) 8.16 (m, 1 H)  
8.18 (dd, *J*=8.1, 1.0 Hz, 1 H) 8.57 (s, 1 H).

B. (7-nitro-1*H*-benzoimidazol-1-yl)acetonitrile (1.1 g, 5.4 mmol) was dissolved in 18%  
hydrochloric acid (30 mL), the solution was transferred into a vial, which was sealed and  
20 heated at 105 °C for 6 h. The vial was cooled, the volatiles were removed under reduced  
pressure and the residue was co-evaporated two times with acetonitrile. To the residue  
were added dichloromethane (15 mL) and triethylamine (1 mL), and the slurry was  
purified on a silica gel column using a mixture of dichloromethane/methanol/triethylamine  
84:15:1 (v/v/v) as an eluent to yield the title compound, 1.2 g (69%). MS (ESI) *m/z*:  
25 221.98 [M-Et<sub>3</sub>N+H].  
<sup>1</sup>H NMR (400 MHz, DMSO-*D*<sub>6</sub>) □ ppm 1.14 (t, *J*=7.1 Hz, 9 H) 2.97 (q, *J*=7.1 Hz, 6 H)  
5.01 (s, 2 H) 7.36 (t, *J*=8.1 Hz, 1 H) 7.93 (dd, *J*=8.1, 1.0 Hz, 1 H) 8.06 (m, 1 H) 8.37 (s, 1  
H).



**2-(7-Nitro-1H-benzoimidazol-1-yl)propionic acid triethylammonium salt**



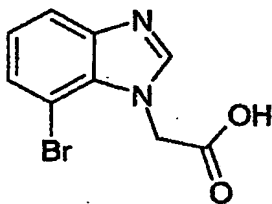
**5 A. 2-(7-nitro-1H-benzoimidazol-1-yl)propanenitrile**

The compound was synthesised from 4(7)-nitro-1H-benzoimidazole (1.0 g, 6.1 mmol) and 2-bromopropanenitrile (0.58 mL, 6.5 mmol) according to the procedure described for the synthesis of (7-Nitro-1H-benzoimidazol-1-yl)acetic acid triethylammonium salt, part A, in a 0.14 g (11%) yield. MS (ESI)  $m/z$ : 217.16  $[M+H]$ .  $^1H$  NMR (400 MHz, DMSO- $D_6$ )  $\square$

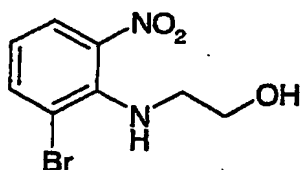
10 ppm 2.01 (d,  $J=7.0$  Hz, 3 H) 6.08 (q,  $J=7.1$  Hz, 1 H) 7.48 (t,  $J=8.1$  Hz, 1 H) 8.09 (m, 1 H) 8.16 (dd,  $J=8.0, 1.0$  Hz, 1 H) 8.89 (s, 1 H).

B. The title compound was synthesized from 2-(7-nitro-1H-benzoimidazol-1-yl)propanenitrile according to the procedure described for the synthesis of (7-Nitro-1H-benzoimidazol-1-yl)acetic acid triethylammonium salt, part B, in 0.15 g (69%) yield. MS

15 (ESI)  $m/z$ : 236.08  $[M-Et_3N+H]$ .

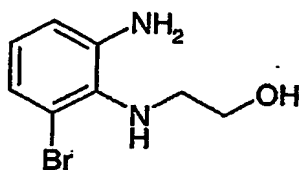


**(7-Bromo-1H-benzoimidazol-1-yl)acetic acid**



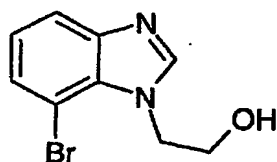
A. 2-[(2-bromo-6-nitrophenyl)amino]ethanol

A solution of 1-bromo-2-chloro-3-nitrobenzene (0.34 g, 1.4 mmol) and ethanolamine (0.22 mL, 3.5 mmol) in dry ethanol (3.8 mL) was irradiated in a microwave oven at 135 °C for 180 min. After the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, the organic phase was washed with potassium bisulfate (0.1 M), water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Purification was performed using flash chromatography on a silica column and 25% ethyl acetate in heptane as an eluent to yield 2-[(2-bromo-6-nitrophenyl)amino]ethanol as red oil, 0.24 g (65%). <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>)  $\delta$  ppm 3.13 (q, *J*=5.2 Hz, 2 H) 3.51 (q, *J*=5.1 Hz, 2 H) 4.87 (t, *J*=5.1 Hz, 1 H) 6.18 (t, *J*=5.1 Hz, 1 H) 6.80 (t, *J*=8.1 Hz, 1 H) 7.84 (dd, *J*=7.8, 3.3 Hz, 2 H).



B. 2-[(2-amino-6-bromophenyl)amino]ethanol

To a solution of 2-[(2-bromo-6-nitrophenyl)amino]ethanol (1.95 g, 7.5 mmol) in a mixture of methanol (30 mL) and water (15 mL) sodium acetate trihydrate (56 g) was added. To this mixture titanium trichloride (65 mL, as 15% solution in 10% aqueous HCl) was added drop-wise over period of 20 min. The resulting dark solution was allowed to stir for additional 2 h, and then carefully neutralized with saturated aqueous sodium bicarbonate. The solids were filtered off, and washed with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated yielding 2-[(2-amino-6-bromophenyl)amino]ethanol as pale-yellow oil (1.61 g, 93%) that was used in the next step without further purification. MS (ESI) *m/z*: 231.01 [M+H].

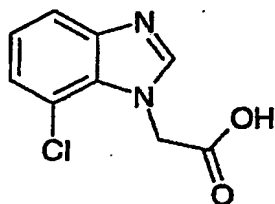


C. 2-(7-Bromo-1*H*-benzoimidazol-1-yl)ethanol

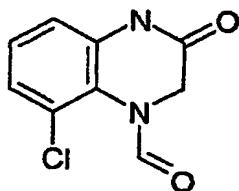
2-[(2-Amino-6-bromophenyl)amino]ethanol (0.14 g, 0.54 mmol) was dissolved in formic acid (3 mL) and irradiated in microwave oven at 135 °C for 2 h. The mixture was cooled and treated with 37% hydrochloric acid (1 mL) at 50°C for 0.5 h. The volatiles were removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was washed with water and brine, dried over sodium sulfate and concentrated to yield 2-(7-Bromo-1*H*-benzoimidazol-1-yl)ethanol, 0.14 g (90%). MS (ESI)  $m/z$ : 241.09  $[M+H]^+$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.76 (q,  $J=5.5$  Hz, 2 H) 4.55 (t,  $J=5.4$  Hz, 2 H) 4.97 (t,  $J=5.4$  Hz, 1 H) 7.12 (m, 1 H) 7.43 (m, 1 H) 7.66 (dd,  $J=8.0, 1.0$  Hz, 1 H) 8.19 (s, 1 H).

D. To a solution of 2-(7-bromo-1*H*-benzoimidazol-1-yl)ethanol (1.1 g, 4.6 mmol) in acetone (150 mL) Jones reagent (a mixture of  $CrO_3$  0.5 g, 5 mmol;  $H_2SO_4$  0.5 mL in a minimal amount of water to form a clear solution) was added. The reaction mixture was stirred for 6 h, quenched with 2-propanol (2 mL) and concentrated to a quarter of the initial volume. The residue was partitioned between ethyl acetate and aqueous potassium hydrosulfate (0.1 M). The aqueous phase was extracted 3-4 times with ethyl acetate and the combined organic extract was washed with brine, dried over  $Na_2SO_4$  and concentrated. The oily residue was dissolved in a mixture of dichloromethane (15 mL) and triethylamine 2 mL)

and the resulting slurry was loaded onto a flash silica column and eluted with a mixture of dichloromethane/methanol/triethylamine 84:15:1. Fractions containing product were pooled, diluted with dioxane (20 mL), evaporated to dryness and dried in vacuo at 40 °C to yield the title product, 0.79 g (48%). MS (ESI)  $m/z$ : 254.99  $[M-Et_3N+H]^+$ .  $^1H$  NMR (400 MHz, DMSO- $D_6$ )  $\delta$  ppm 5.28 (s, 2 H) 7.14 (t,  $J=7.8$  Hz, 1 H) 7.42 (d,  $J=7.6$  Hz, 1 H) 7.67 (d,  $J=8.1$  Hz, 1 H) 8.24 (s, 1 H).



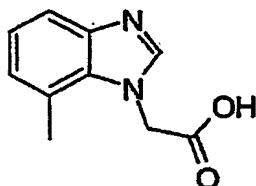
(7-Bromo-1H-benzotriazol-1-yl)acetic acid



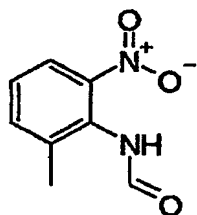
A. 8-Chloro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carbaldehyde

- 5 To a solution of *N*-(2-chloro-6-nitrophenyl)glycine (300 mg, 1.30 mmol) in formic acid (16 mL) tin chloride (1.47 g, 6.50 mmol) was added at 60 °C, and the mixture was stirred at this temperature for 1.5h. The volatiles were removed *in vacuo*, and the residue was partitioned between a 1 M solution of sodium hydroxide and ethyl acetate. The organic phase was dried over magnesium sulfate, and concentrated. The crude product was purified
- 10 by column chromatography using heptane/ethyl acetate, 1:1 as an eluent affording 8-chloro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carbaldehyde (89 mg). MS (ESI) *m/z*: 209.2 [M-H]. <sup>1</sup>H NMR (400 MHz, acetone-D<sub>6</sub>) δ ppm 4.42 (s, 2 H), 7.12 (dd, *J*=1.5, 7.6 Hz, 1H), 7.22 (dd, *J*=1.5, 8.1 Hz, 1H), 7.27 (t, *J*=8.1 Hz, 1H), 8.62 (s, 1H), 9.8 (br.s, 1H)

- B. 8-Chloro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carbaldehyde (89 mg) was dissolved in a mixture of formic acid (1 mL) and 37% hydrochloric acid (1 mL) and the mixture was heated at 100-105°C for 6 h. The volatiles were removed *in vacuo*, and the residue was co-evaporated several times with acetonitrile affording 100 mg (31%) of the title compound as white crystalline powder. MS (ESI) *m/z*: 211.0 [M+H]. <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ ppm 5.38 (s, 2 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 8.63 (s, 1 H)
- 20

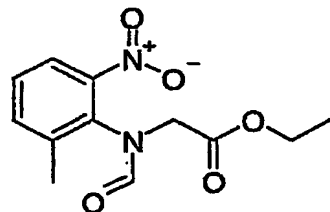


(7-Methyl-1H-benzimidazol-1-yl)acetic acid



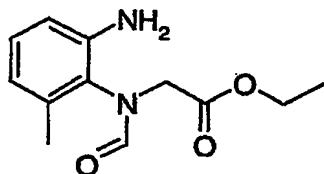
5 A. (2-Methyl-6-nitrophenyl)formamide

Formic acid (0.97 g, 21.0 mmol) was added to acetic anhydride (1.74 g, 17.1 mmol) and the mixture was heated at 50 °C for 0.5 h. 2-Methyl-6-nitroaniline (1.0 g, 6.57 mmol) was added, and the mixture was heated at 50 °C for additional 1.5 h. Volatiles were removed *in vacuo*, and the residue was partitioned between water and ethyl acetate. The organic phase  
10 was washed with a saturated solution of sodium bicarbonate and brine, dried over magnesium sulfate. The volatiles were removed *in vacuo* affording 1.10 g of a solid residue. The crude product was recrystallized from ethyl acetate/heptane (1:1) affording 0.57 g (48% yield) of (2-methyl-6-nitrophenyl)formamide as a white solid. MS (ESI) *m/z* 179 [M-H]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) □ ppm 2.37 (s, 3 H), 7.33 (t, *J* = 8.0 Hz, 1 H),  
15 7.56 (d, *J* = 7.3 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 8.50-8.20 m (2 H)



B. Ethyl *N*-formyl-*N*-(2-methyl-6-nitrophenyl)glycinate

To a mixture of (2-methyl-6-nitrophenyl)formamide (180 mg, 1.0 mmol), potassium carbonate (276 mg, 2.0 mmol), potassium iodide (5 mg) and *N,N*-dimethylformamide (1 mL) a solution of ethyl bromoacetate (184 mg, 1 mmol) in *N,N*-dimethylformamide (1 mL) was added at room temperature. The mixture was heated at 60 °C for 3 h, then cooled to room temperature. The mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with brine and dried over magnesium sulfate. The volatiles were removed *in vacuo*. The crude product was purified by column chromatography using heptane/ethyl acetate (70:30→50:50) as an eluent affording ethyl *N*-formyl-*N*-(2-methyl-6-nitrophenyl)glycinate, 167 mg (63% yield) as an oil. MS (ESI)  $m/z$  267 [M+H].



C. Ethyl *N*-(2-amino-6-methylphenyl)-*N*-formylglycinate

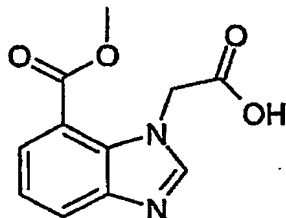
A solution of ethyl *N*-formyl-*N*-(2-methyl-6-nitrophenyl)glycinate (154 mg, 0.58 mmol) in methanol containing 5% Pd/C (35 mg) was hydrogenated at 1 atmosphere for 1 h. The mixture was filtered through a pad of celite, and the solvent was removed *in vacuo* affording ethyl *N*-(2-amino-6-methylphenyl)-*N*-formylglycinate, 127 mg (93%) as an oil. MS (ESI)  $m/z$  237 [M+H]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.30 (t,  $J$  = 7.2 Hz, 3 H), 2.14 (s, 3 H), 3.60 (d,  $J$  = 17 Hz, 1 H), 4.32–4.18 (m, 2 H), 4.70 (br. s, 2 H), 4.77 (d,  $J$  = 17 Hz, 1 H), 6.60 (app t,  $J$  = 8.0 Hz, 2 H), 7.05 (t,  $J$  = 7.8 Hz, 1 H), 8.11 (s, 1 H).

D. A solution of ethyl *N*-(2-amino-6-methylphenyl)-*N*-formylglycinate (115 mg, 0.49 mmol) in formic acid (5 mL) was heated at reflux for 1 h, then allowed to cool to room temperature. The volatiles were removed *in vacuo*. The residue was dissolved in hydrochloric acid (6 M, 4 mL) and the solution was heated at reflux for 1 h. The volatiles were removed *in vacuo*, and the residue was co-evaporated several times with acetonitrile.

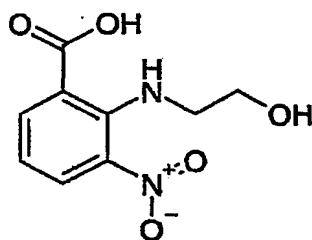


The residue was suspended in acetonitrile, filtered, and dried *in vacuo* affording the title compound, 96 mg (86%) as a solid. MS (ESI)  $m/z$  189 [M-H].  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{D}_6$ )  $\delta$  ppm 2.63 (s, 3 H), 5.55 (s, 2H), 7.34 (d,  $J = 7.3$  Hz, 1 H), 7.46 (t,  $J = 7.8$  Hz, 1 H), 7.71 (d,  $J = 8.3$  Hz, 1 H), 9.43 (s, 1 H)

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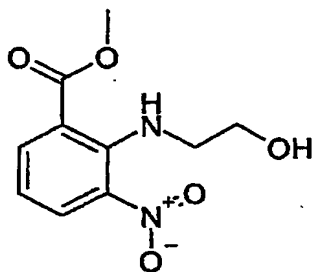


**3-Carboxymethyl-3H-benzimidazole-4-carboxylic acid methyl ester**



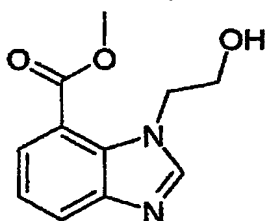
**A. 2-(2-Hydroxyethylamino)-3-nitrobenzoic acid**

- 10 2-Chloro-3-nitrobenzoic acid (5.0g, 24.8 mmol) was suspended in ethanol (90 mL) and ethanolamine (4.5 mL, 74.8 mmol) was added. The resulting clear solution was heated at 100°C for two days. The volatiles were removed under reduced pressure. The residue was treated with water (40 mL) and the mixture was acidified with 1M hydrochloric acid to pH 2. A yellow precipitate formed was collected by filtration and washed with water to yield
- 15 2-(2-hydroxyethylamino)-3-nitrobenzoic acid, 5.14g (92%). MS (ESI)  $m/z$  225 [M-H].  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 3.04 (t,  $J=5.31$  Hz, 2 H), 3.69 (t,  $J=5.31$  Hz, 2 H), 6.71 (t,  $J=7.96$  Hz, 1 H), 7.93 (dd,  $J=8.21, 1.64$  Hz, 1 H), 8.13 (dd,  $J=7.71, 1.64$  Hz, 1 H)



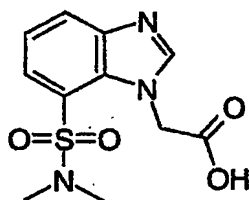
**B. 2-(2-Hydroxyethylamino)-3-nitrobenzoic acid methyl ester**

2-(2-Hydroxyethylamino)-3-nitrobenzoic acid (5.14g, 22.7 mmol) was dissolved in methanol (200 mL) and concentrated H<sub>2</sub>SO<sub>4</sub> (10 mL) was added. The mixture was heated at reflux for 2.5 h. The solvent was removed at reduced pressure. The residue was treated with water (100 mL) and extracted with ethyl acetate (3x150 mL). The combined organic phase was dried and concentrated. Purification by column chromatography on silica using heptane ethyl acetate 1:1 as an eluent afforded 2-(2-hydroxyethylamino)-3-nitrobenzoic acid methyl ester, 3.92g (72%). MS (ESI) *m/z* 241 [M+H]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 3.12 (t, *J*=5.10 Hz, 2 H), 3.84 (t, *J*=5.15 Hz, 2 H), 3.91 (s, 3 H), 6.69 (t, *J*=7.96 Hz, 1 H), 7.95 (dd, *J*=8.34, 1.52 Hz, 1 H), 8.08 (dd, *J*=7.83, 1.52 Hz, 1 H)

**C. 3-(2-Hydroxyethyl)-3H-benzimidazole-4-carboxylic acid methyl ester**

Suspension of 2-(2-Hydroxyethylamino)-3-nitrobenzoic acid methyl ester (3.06g, 12.7 mmol) in methanol (130 mL) was hydrogenated at atmospheric pressure over 10% palladium on activated charcoal for 10 minutes. The mixture was filtered through a pad of Celite and the solvent was removed in vacuum. The residue was dissolved in formic acid (60 mL) and heated at 100°C for 45 minutes and then kept at ambient temperature overnight. Excess of the formic acid was removed under reduced pressure. The residue was dissolved in methanol (100 mL) and treated with concentrated ammonia in methanol (20 mL) for 50 minutes followed by evaporation of the volatiles. Purification by column chromatography on silica using dichloromethane in methanol 95:5 afforded 3-(2-hydroxyethyl)-3H-benzimidazole-4-carboxylic acid methyl ester, 2.31 g (83%). MS (ESI) *m/z* 221 [M+H]. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 3.78 (t, *J*=5.05 Hz, 2 H), 3.96 (s, 3 H), 4.70 (t, *J*=5.05 Hz, 2 H), 7.33 (t, *J*=7.83 Hz, 1 H), 7.84 - 7.91 (m, 2 H), 8.20 (s, 1 H)

D. To a solution of 3-(2-hydroxyethyl)-3*H*-benzoimidazole-4-carboxylic acid methyl ester (2.83g, 12.8 mmol) in acetone (140 mL) a solution of CrO<sub>3</sub> (1.77g, 17.7 mmol) and concentrated H<sub>2</sub>SO<sub>4</sub> (1.77 mL) in water (5 mL) was added. The resulting yellow solution  
5 was stirred at ambient temperature for 1 h, while the mixture had changed colour to blue green, and then was quenched by the addition of isopropanol. The volatiles were removed in vacuum. The residue was treated with brine and pH of the solution was adjusted to 3 by addition of aqueous sodium bicarbonate. The water phase was repeatedly extracted with ethyl acetate containing 5% methanol. Drying of the organic phase with sodium sulfate,  
10 evaporation of solvent and purification of the residue by column chromatography on silica using a gradient of 10-25% methanol in dichloromethane afforded the title compound, 1.44g (48%). MS (ESI) *m/z* 235 [M+H]. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm 3.95 (s, 3 H), 5.17 (s, 2H), 7.57 (t, *J*=7.95 Hz, 1 H), 7.96-8.05 (m, 2 H), 8.79 (s, 1 H)



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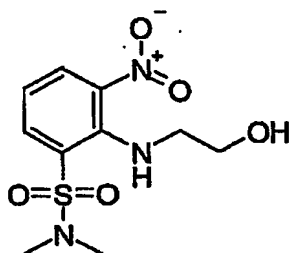
(7-Dimethylsulfamoyl-benzoimidazol-1-yl)-acetic acid



A. 2-Chloro-*N,N*-dimethyl-3-nitrobenzenesulfonamide

20 2-Chloro-3-nitrobenzenesulfonyl chloride (235 mg, 0.918 mmol) was treated with a 2 M solution of dimethylamine in methanol (0.55 mL, 1.10 mmol), and triethylamine (0.13 mL, 0.918 mmol) in methanol (1 mL), and the suspension was stirred at room temperature for 2.5 h. The volatiles were removed *in vacuo*, and the residue was purified by column

chromatography using heptane/ethyl acetate, 70:30→50:50 as an eluent, affording 2-chloro-*N,N*-dimethyl-3-nitrobenzenesulfonamide, 202 mg (83%) as a white solid. MS (ESI)  $m/z$  265 [M+H].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 2.95 (s, 6 H); 7.56 (t,  $J = 8.0$  Hz, 1 H), 7.88 (dd,  $J = 8.1, 1.5$  Hz, 1 H), 8.31 (dd,  $J = 8.1, 1.5$  Hz, 1 H)

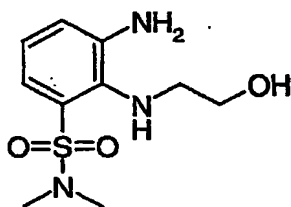


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B. 2-[(2-Hydroxyethyl)amino]-*N,N*-dimethyl-3-nitrobenzenesulfonamide

A solution of 2-chloro-*N,N*-dimethyl-3-nitrobenzenesulfonamide (170 mg, 0.642 mmol) and ethanolamine (196 mg, 3.21 mmol) in ethanol (6 mL) was heated at reflux for 4 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography using heptane/ethyl acetate, 1:1 as an eluent affording 2-[(2-hydroxyethyl)amino]-*N,N*-dimethyl-3-nitrobenzenesulfonamide, 161 mg (87%). MS (ESI)  $m/z$  288 [M-H].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.92 (t,  $J = 5.6$  Hz, 1 H), 2.83 (s, 6 H), 3.10-3.06 (m, 2 H), 3.84-3.80 (m, 2 H), 6.83 (t,  $J = 8.0$  Hz, 1 H), 6.87 (broad s, 1 H), 7.91-7.87 (m, 2 H)

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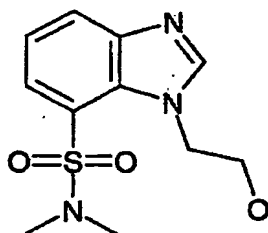


C. 3-Amino-2-[(2-hydroxyethyl)amino]-*N,N*-dimethylbenzenesulfonamide

To a solution of 2-[(2-hydroxyethyl)amino]-*N,N*-dimethyl-3-nitrobenzenesulfonamide (107 mg, 0.37 mmol) in methanol (2 mL) a solution of 85% sodium hydrosulfite (0.30 g, 1.5 mmol) in water (1.2 mL) was added. The obtained suspension was heated at 60 °C for 10 min. The volatiles were removed *in vacuo*, and the residue was partitioned between a saturated solution of sodium bicarbonate and ethyl acetate. The organic phase was dried

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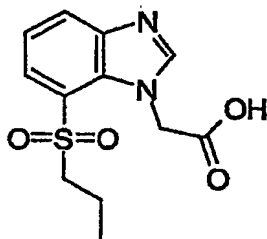
over magnesium sulfate and concentrated *in vacuo* affording 3-amino-2-[(2-hydroxyethyl)amino]-*N,N*-dimethylbenzenesulfonamide, 69 mg (72 %) as an oil: MS (ESI)  $m/z$  260 [M+H].



5 D. 3-(2-Hydroxyethyl)-3H-benzoimidazole-4-sulfonic acid dimethylamide

A solution of 3-amino-2-[(2-hydroxyethyl)amino]-*N,N*-dimethylbenzenesulfonamide (69 mg, 0.266 mmol) in formic acid (2 mL) and 2 M hydrochloric acid (2 mL) was heated at reflux for 1 h. The volatiles were removed *in vacuo*, and the residue was partitioned between an aqueous sodium hydroxide solution and ethyl acetate. The organic phase was  
10 dried over magnesium sulfate and concentrated *in vacuo* affording 3-(2-hydroxyethyl)-3H-benzoimidazole-4-sulfonic acid dimethylamide, 66 mg. MS (ES)  $m/z$  270 [M+H]<sup>+</sup>.

E. To a solution of 3-(2-hydroxyethyl)-3H-benzoimidazole-4-sulfonic acid dimethylamide (66 mg) in acetone (3 mL) 2.6 M solution of Jones reagent (0.28 mL, 0.74 mmol; a stock  
15 solution was prepared by dissolving 0.52 g of CrO<sub>3</sub> and 0.52 mL of concentrated H<sub>2</sub>SO<sub>4</sub> in water to a total volume of 2.0 mL) was added. The reaction mixture was stirred at room temperature for 2 h, then quenched with 2-propanol. The volatiles were removed *in vacuo*. The residue was treated with brine, and basicified with aqueous solution of sodium hydroxide to pH 4. The aqueous phase was extracted twice with ethyl acetate. The  
20 combined organic phase was dried over magnesium sulfate and concentrated affording the title compound, 51 mg (74%). MS (ES)  $m/z$  282 [M-H].

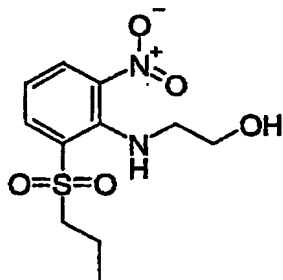


## [7-(Propane-1-sulfonyl)-benzoimidazol-1-yl]-acetic acid



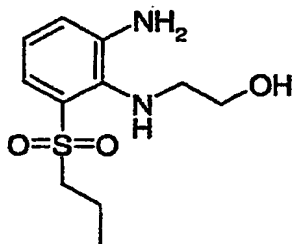
## A. 2-Chloro-1-nitro-3-(propylsulfonyl)benzene

- 5 To an ice-cooled solution of 2-chloro-1-nitro-3-(propylthio)benzene (0.71 g, 3.06 mmol) in *N,N*-dimethylformamide (10 mL) *m*-chloroperbenzoic acid (2.1 g, 9.19 mmol) was added in portions. The ice-bath was removed, and the reaction mixture was stirred at ambient temperature for 24 h. The volatiles were removed *in vacuo*. The residue was treated with 1 M solution of sodium hydroxide and extracted with ethyl acetate. The organic phase was
- 10 dried over magnesium sulfate and concentrated to leave a crude product, 0.88 g as an oil. Purification by column chromatography on silica using heptane/ethyl acetate, 70:30 as an eluent afforded 2-chloro-1-nitro-3-(propylsulfonyl)benzene, 657 mg (81%) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.06 (t, *J* = 7.4 Hz, 3H), 1.84–1.74 (m, 2 H), 3.45–3.41 (m, 2 H), 7.65 (t, *J* = 8.1 Hz, 1 H), 7.99 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.37 (dd, *J* =
- 15 8.1, 1.5 Hz, 1 H)



## B. 2-([2-Nitro-6-(propylsulfonyl)phenyl]amino)ethanol

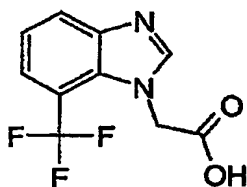
The compound was synthesized in 99% yield according to the procedure described for the synthesis of (7-dimethylsulfamoyl-benzoimidazol-1-yl)-acetic acid, part B, starting from 2-chloro-1-nitro-3-(propylsulfonyl)benzene. MS (ESI)  $m/z$  289 [M+H].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.02 (t,  $J = 7.4$  Hz, 3 H), 1.80-1.70 (m, 3 H), 3.13-3.09 (m, 2 H), 3.27-3.23 (m, 2 H), 3.87-3.84 (m, 2 H), 6.88 (t,  $J = 8.0$  Hz, 1 H), 6.95 (broad s, 1 H), 7.91 (dd,  $J = 8.1, 1.5$  Hz, 1 H), 7.99 (dd,  $J = 7.8, 1.8$  Hz, 1 H)

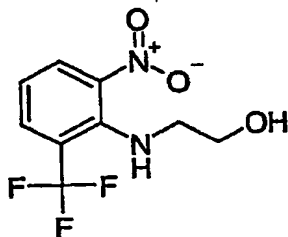


10 C. 2-([2-Amino-6-(propylsulfonyl)phenyl]amino)ethanol

The compound was synthesized in 52% yield according to the procedure described for the synthesis of (7-dimethylsulfamoyl-benzoimidazol-1-yl)-acetic acid, part C, starting from 2-([2-nitro-6-(propylsulfonyl)phenyl]amino)ethanol. MS (ESI)  $m/z$  259 [M+H].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ )  $\delta$  ppm 1.00 (t,  $J = 7.3$  Hz, 3 H), 1.82-1.72 (m, 2 H), 3.15-3.11 (m, 2 H), 3.29-3.27 (m, 2 H), 3.80-3.77 (m, 2 H), 6.92-6.90 (m, 1 H), 6.96 (t,  $J = 7.8$  Hz, 1 H), 7.23 (dd,  $J = 7.7, 1.6$  Hz, 1 H)

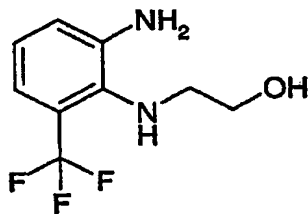
D. The title compound was synthesized according to the procedure described for the synthesis of (7-dimethylsulfamoyl-benzoimidazol-1-yl)-acetic acid, part D and E, starting from 2-([2-amino-6-(propylsulfonyl)phenyl]amino)ethanol. MS (ESI)  $m/z$  281 [M-H].



**[7-(Trifluoromethyl)-1H-benzimidazol-1-yl]acetic acid****A. 2-([2-Nitro-6-(trifluoromethyl)phenyl]amino)ethanol**

To a suspension of sodium perborate tetrahydrate (7.69 g, 50 mmol) in acetic acid (30 mL) a solution of 3-amino-2-nitrobenzotrifluoride (2.06 g, 10 mmol) in acetic acid (25 mL) was added dropwise at 55 °C over 1.5 h. The mixture was stirred at 55 °C overnight.

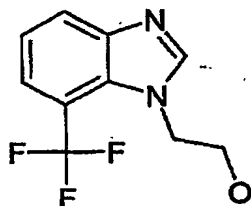
Precipitated material was filtered off, and the filtrate was concentrated in vacuo. The residue was suspended in 2 M hydrochloric acid and filtered. The precipitate was washed with 2 M hydrochloric acid and water, then dried in vacuum at room temperature affording a yellow solid, 1.14 g. This material was suspended in ethanol (10 mL), and a solution of ethanolamine (1.10 g, 18.1 mmol) in ethanol (10 mL) was added. The reaction mixture was heated at reflux for 20 min, and then allowed to cool to room temperature. The volatiles were removed in vacuo. The residue was purified by column chromatography on silica using heptane/ethyl acetate, 80:20 as an eluent affording 0.72 g (29% yield) of 2-([2-nitro-6-(trifluoromethyl)phenyl]amino)ethanol as an orange oil. MS (ESI)  $m/z$  249 [M-H].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 3.38-3.34 (m, 2 H), 3.85-3.82 (m, 2 H), 6.88-6.84 (m, 2 H), 7.77 (dd,  $J = 7.8, 1.3$  Hz, 1 H), 8.11 (dd,  $J = 8.3, 1.5$  Hz, 1 H)

**B. 2-(2-Amino-6-trifluoromethyl-phenylamino)-ethanol**

To a solution of 2-([2-nitro-6-(trifluoromethyl)phenyl]amino)ethanol (0.72 g, 2.88 mmol) in methanol (30 mL) a suspension of 85% sodium hydrosulfite (2.0 g, 9.8 mmol) in water (6 mL) was added. Additional water (4 mL) was added, and the mixture was heated at 60 °C for 15 min. The reaction mixture was cooled and concentrated in vacuo. The residue



was extracted with ethyl acetate, and the organic phase was dried over magnesium sulfate. The solvent was removed in vacuo affording 0.57 g of 2-(2-amino-6-trifluoromethyl-phenylamino)-ethanol: MS (ES)  $m/z$  219  $[M-H]^+$ .



5 C. 2-[7-(Trifluoromethyl)-1H-benzimidazol-1-yl]ethanol

A solution of 2-(2-amino-6-trifluoromethyl-phenylamino)-ethanol (0.57 g) in formic acid (20 mL) was heated at reflux for 20 min. The excess of formic acid was removed in vacuo; the residue was dissolved in a 2 M hydrochloric acid, and heated at reflux for 10 min. The solution was concentrated in vacuum and the residue was co-evaporated with acetonitrile  
10 and ethanol. The residue was treated with a saturated solution of sodium bicarbonate and extracted twice with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The crude product was purified by column chromatography on silica using ethyl acetate as an eluent affording 2-[7-(trifluoromethyl)-1H-benzimidazol-1-yl]ethanol, 0.36 g (55% yield) as a white solid. MS (ESI)  $m/z$  231  
15  $[M+H]^+$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 3.74-3.70 (m, 2 H), 4.37 (t,  $J$  = 5.3 Hz, 2 H), 5.06 (t,  $J$  = 4.8 Hz, 1 H), 7.39 (t,  $J$  = 7.8 Hz, 1 H), 7.67 (d,  $J$  = 7.8 Hz, 1 H), 8.01 (d,  $J$  = 8.1 Hz, 1 H), 8.33 (s, 1 H)

D. To a solution of 2-[7-(trifluoromethyl)-1H-benzimidazol-1-yl]ethanol (55 mg, 0.239  
20 mmol) in acetone (4 mL) a 2.6 M solution of Jones reagent (0.28 mL, 0.72 mmol; a stock solution was prepared by dissolving 0.52 g of  $CrO_3$  and 0.52 mL of conc.  $H_2SO_4$  in water to a total volume of 2.0 mL) was added. The mixture was stirred at room temperature for 30 min. Another 0.1 mL of Jones reagent was added, and the mixture was stirred for a further 15 min. The reaction mixture was quenched by dropwise addition of 2-propanol  
25 (0.2 mL), stirred for 5 min, and then decanted. Remaining chromium salts were washed with 2-propanol. The combined organic phase was concentrated in vacuum. The residue was treated with brine and basicified with 1M solution of sodium hydroxide to pH 4. The water phase was extracted twice with ethyl acetate. The organic phase was dried over

magnesium sulfate and concentrated in vacuum affording the title compound (42 mg) as a solid. MS (ESI)  $m/z$  243 [M-H].

### Synthesis of the target compounds

#### General method.

To an ice-cooled solution of a 7-substituted (1*H*-benzimidazol-1-yl)acetic acid, prepared as described above (0.14 mmol), triethylamine (0.80 mL, 0.56 mmol) and an appropriate amine (0.2 mmol) in acetonitrile (2 mL) *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluoro-phosphate (69 mg, 0.18 mmol) ) was added. The ice-bath was removed, and the reaction mixture was stirred at ambient temperature for 0.5 – 2 h. The mixture was quenched with methanol and the volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica using a solution of 0-10% methanol in ethyl acetate as an eluent affording the title compound. Alternatively the residue was purified by preparative HPLC on XTerra C<sub>8</sub> column (19×300 mm) using 0.1 M aqueous NH<sub>4</sub>OAc/CH<sub>3</sub>CN as an eluent.

Example number	Name	MW calcd	MW found [M+1] or [M-1]	<sup>1</sup> H NMR
1	N-(3-Fluoro-4-methoxy-phenyl)-2-(7-nitro-1 <i>H</i> -benzoimidazol-1-yl)-acetamide	344.3	345.1	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 3.79 (s, 3H), 5.30 (s, 2H), 6.82 – 6.92 (m, 1H), 7.10 – 7.19 (m, 1H), 7.28 – 7.42 (m, 2H), 8.01 – 8.13 (m, 3H)
2	N-(2-Fluoro-4-trifluoromethylphenyl)-2-(7-nitro-1 <i>H</i> -benzoimidazol-1-yl)-acetamide	382.4	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.42 (s, 2H), 7.27 – 7.40 (m, 3H), 8.02 – 8.11 (m, 3H), 8.12 – 8.23 (m, 1H)

3	<b>N-(3-Chloro-4-iodo-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	456.6	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.27 (s, 2H), 7.08 (dd, J=2.5, 8.6 Hz, 1H), 7.33 (t, J=8.1 Hz, 1H), 7.65 (d, J=8.6 Hz, 1H), 7.68 (d, J=2.5 Hz, 1H), 7.99 – 8.04 (m, 3H)
4	<b>N-(3-Chloro-4-methoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	360.8	no	(400 MHz, DMSO-d <sub>6</sub> ) □ ppm 3.80 (s, 3H), 5.37 (s, 2H), 7.11 (d, J=9.1 Hz, 1H), 7.36 (dd, J=2.5, 9.1 Hz, 1H), 7.42 (t, J=8.1 Hz, 1H), 7.64 (d, J=2.5 Hz, 1H), 8.02 (d, J=8.1 Hz, 1H), 8.13 (dd, J=1.0, 8.1 Hz, 1H), 8.44 (s, 1H), 10.4 (br.s, 1H)
5	<b>N-(3-Difluoromethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	362.3	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.30 (s, 2H), 6.45 (t, J=7.4 Hz, 1H), 6.74 – 6.82 (m, 1H), 7.16 – 7.30 (m, 3H), 7.31 – 7.40 (m, 1H), 8.00 – 8.09 (m, 2H), 8.09 – 8.17 (m, 1H)
6	<b>N-(3-Methoxy-5-trifluoromethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	394.3	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 3.73 (s, 3H), 5.32 (s, 2H), 6.80 (br.s, 1H), 7.24 (br.s, 1H), 7.35 (t, J=8.1 Hz, 1H), 7.38 (br.s, 1H), 8.01 – 8.08 (m, 2H), 8.15 (br.s, 1H)
7	<b>N-(3,5-Difluoro-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	332.3	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.32 (s, 2H), 6.43 – 6.52 (m, 1H), 7.03 – 7.13 (m, 2H), 7.33 – 7.42 (m, 1H), 8.01 –

				8.10 (m, 2H), 8.19 (s, 1H)
8	2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethoxy-phenyl)-acetamide	380.3	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.29 (s, 2H), 7.07 (d, J=8.8 Hz, 2H), 7.33 (t, J=8.1 Hz, 1H), 7.47 (d, J=8.9 Hz, 2H), 8.00 – 8.06 (m, 2H), 8.08 (s, 1H)
9	N-(3-Methoxy-5-trifluoromethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	394.3	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 3.73 (s, 3H), 5.32 (s, 2H), 6.80 (br.s, 1H), 7.24 (br.s, 1H), 7.35 (t, J=8.1 Hz, 1H), 7.38 (br.s, 1H), 8.01 – 8.08 (m, 2H), 8.15 (br.s, 1H)
10	2-(7-Nitro-1H-benzoimidazol-1-yl)-N-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-acetamide	412.3	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.32 (s, 2H), 5.85 (t, J=5.2 Hz, 1H), 6.85 – 6.92 (m, 1H), 7.18 – 7.35 (m, 3H), 7.43 (s, 1H), 7.99 – 8.08 (m, 2H), 8.14 (s, 1H)
11	N-(4-tert-Butyl-phenyl)-2-(7-nitrobenzoimidazol-1-yl)-acetamide	352.4	no	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 1.22 (s, 9H), 5.29 (s, 2H), 7.24 (d, J=8.6 Hz, 2H), 7.34 (d, J=8.7 Hz, 3H), 7.99 – 8.05 (m, 2H), 8.10 (s, 1H)
12	N-[3-(1-Hydroxy-ethyl)-phenyl]-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	340.3	341.2	(400 MHz, CD <sub>3</sub> CN) □ ppm 1.36 (d, J=6.1 Hz, 3H), 4.72 – 4.79 (m, 1H), 5.30 (s, 2H), 7.07 (d, J=7.6 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.33 – 7.37 (m, 1H), 7.36 (t, J=8.1 Hz, 1H), 7.46 – 7.48 (m, 1H), 8.01 (d,

				J=8.1 Hz, 1H), 8.06 (dd, J=1.1, 8.1 Hz, 1H), 8.06 (s, 1H), 8.55 (br.s, 1H)
13	<b>2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethyl-phenyl)-acetamide</b>	364.3	365.0	(400 MHz, DMSO-d <sub>6</sub> ) □ ppm 5.44 (s, 2H), 7.43 (t, J=8.1 Hz, 1H), 7.68 (d, 8.4 Hz, 2H), 7.73 (d, J=8.4 Hz, 2H), 8.03 (d, J=8.1 Hz, 1H), 8.15 (d, J=8.1 Hz, 1H), 8.45 (s, 1H), 10.8 (br.s, 1H)
14	<b>N-(3-Chloro-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	330.7	no	(400 MHz, CD <sub>3</sub> CN) □ ppm 5.32 (s, 2H), 7.10 – 7.14 (m, 1H), 7.28 – 7.33 (m, 1H), 7.36 – 7.40 (m, 1H), 7.41 (t, J=8.1 Hz, 1H), 7.52 – 7.65 (m, 1H), 8.04 (d, J=8.1 Hz, 1H), 8.09 (dd, J=1.0, 8.1 Hz, 1H), 8.11 (s, 1H), 8.78 (br.s, 1H)
15	<b>N-Hexyl-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	304.4	305.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 0.88 (t, J=7.1 Hz, 3H), 1.23 – 1.33 (m, 6H), 1.38 – 1.46 (m, 2H), 3.08 – 3.14 (m, 2H), 5.09 (s, 2H), 6.58 (br.s, 1H), 7.36 (t, J=8.1 Hz, 1H), 7.98 (dd, J=1.0, 8.1 Hz, 1H), 8.04 (s, 1H), 8.05 (dd, J=1.0, 8.1 Hz, 1H)
16	<b>N-(3,4-Difluoro-phenyl)-2-(7-nitrobenzoimidazol-1-yl)-acetamide</b>	332.3	333.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 5.29 (s, 2H), 7.07 – 7.17 (m, 2H), 7.37 (t, J=8.1 Hz, 1H), 7.51 – 7.58 (m, 1H), 8.02 (d,

				J=8.1 Hz, 1H), 8.07 (s, 1H), 8.08 (d, J=8.1 Hz, 1H), 8.73 (br.s, 1H)
17	N-(4-Cyano-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	321.3	320.2	(400 MHz, CD <sub>3</sub> CN) □ ppm 5.33 (s, 2H), 7.38 (t, J=8.1 Hz, 1H), 7.59 (d, J=8.9 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H), 8.03 (d, J=8.1 Hz, 1H), 8.07 (s, 1H), 8.08 (d, J=8.0 Hz, 1H), 8.96 (br.s, 1H)
18	N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	354.3	no	(400 MHz, DMSO-d <sub>6</sub> ) □ ppm 4.15 – 4.23 (m, 4H), 5.34 (s, 2H), 6.77 (d, J=8.6 Hz, 1H), 6.87 (dd, J=2.5, 8.6 Hz, 1H), 7.10 (d, J=2.5 Hz, 1H), 7.41 (t, J=8.1 Hz, 1H), 8.01 (dd, J=1.0, 8.1 Hz, 1H), 8.12 (dd, J=1.0, 7.6 Hz, 1H), 8.44 (s, 1H), 10.2 (br.s, 1H)
19	N-(2-Bromo-benzyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	389.2	391.0	(400 MHz, CD <sub>3</sub> CN) □ ppm 4.40 (d, J=6.1 Hz, 2H), 5.21 (s, 2H), 6.99-7.06 (m, 1H), 7.12 – 7.18 (m, 1H), 7.28 – 7.38 (m, 3H), 7.53 (d, J=7.6 Hz, 1H), 7.99 (d, J=8.1 Hz, 1H), 8.04 (d, J=8.1 Hz, 1H), 8.05 (s, 1H)
20	2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethyl-benzyl)-acetamid	378.3	379.0	(400 MHz, CD <sub>3</sub> CN) □ ppm 4.41 (d, J=6.1 Hz, 2H), 5.19 (s, 2H), 7.07 – 7.14 (m, 1H), 7.35 (t, J=8.1 Hz, 1H), 7.44 –

				7.57 (m, 4H), 7.99 (dd, J=1.0, 8.1 Hz, 1H), 8.04 (dd, J=1.0, 8.1 Hz, 1H), 8.05 (s, 1H)
21	N-(4-Methyl-pyridin-2-yl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	311.3	312.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 2.28 (s, 3H), 5.39 (s, 2H), 6.90 (d, J=5.1 Hz, 1H), 7.38 (t, J=8.1 Hz, 1H), 7.75 – 7.82 (m, 1H), 8.03 (d, J=8.1 Hz, 1H), 8.08 (d, J=8.1 Hz, 1H), 8.08 (s, 1H), 8.13 (d, J=5.1 Hz, 1H), 8.87 (br.s, 1H)
22	N-(3-Cyano-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	321.3	322.1	(400 MHz, CDCl <sub>3</sub> /CD <sub>3</sub> OD) □ ppm 5.28 (s, 2H), 7.25 – 7.35 (m, 3H), 7.67 – 7.72 (m, 1H), 7.79 (br.s, 1H), 8.02 (s, 1H), 7.96 – 8.06 (m, 2H)
23	N-(3,5-Dimethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	356.3	357.0	(400 MHz, CDCl <sub>3</sub> ) □ ppm 3.73 (s, 6H), 5.26 (s, 2H), 6.21 – 6.24 (m, 1H), 6.66 – 6.70 (m, 2H), 7.37 (t, J=8.1 Hz, 1H), 7.69 (br.s, 1H), 8.01 (s, 1H), 8.09 (d, J=8.1 Hz, 1H), 8.13 (d, J=8.1 Hz, 1H)
24	N-(3-Methoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	326.3	327.2	(400 MHz, DMSO-d <sub>6</sub> ) □ ppm 3.69 (s, 3H), 5.39 (s, 2H), 6.62 – 6.66 (m, 1H), 7.02 – 7.06 (m, 1H), 7.18 – 7.23 (m, 2H), 7.42 (t, J=8.1 Hz, 1H), 8.02 (d, 8.1 Hz, 1H), 8.13 (dd, J=1.0, 8.1 Hz, 1H), 8.45 (s, 1H), 10.4 (br.s, 1H)

25	N-(3-Ethoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	340.3	341.2	(400 MHz, DMSO-d6) □ ppm 1.28 (t, $J=6.8$ Hz, 3 H) 3.95 (q, $J=6.7$ Hz, 2 H) 5.38 (s, 2 H) 6.62 (dd, $J=7.8, 2.3$ Hz, 1 H) 7.01 (m, 1 H) 7.19 (m, 2 H) 7.42 (t, $J=7.8$ Hz, 1 H) 8.02 (dd, $J=8.1, 1.0$ Hz, 1 H) 8.14 (m, 1 H) 8.45 (s, 1 H) 10.37 (s, 1 H)
26	N-(3,4-Dimethoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	356.3	357.2	(400 MHz, DMSO-d6) □ ppm 3.68 (s, 3 H) 3.70 (s, 3 H) 5.36 (s, 2 H) 6.88 (d, $J=9.1$ Hz, 1 H) 6.99 (dd, $J=8.8, 2.3$ Hz, 1 H) 7.19 (d, $J=2.5$ Hz, 1 H) 7.42 (t, $J=7.8$ Hz, 1 H) 8.01 (d, $J=7.6$ Hz, 1 H) 8.13 (m, 1 H) 8.45 (s, 1 H) 10.24 (s, 1 H)
27	2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3,4,5-trimethoxy-phenyl)-acetamide	386.4	387.2	(400 MHz, DMSO-d6) □ ppm 3.60 (s, 3 H) 3.70 (s, 6 H) 5.37 (s, 2 H) 6.88 (s, 2 H) 7.42 (t, $J=8.1$ Hz, 1 H) 8.02 (d, $J=8.1$ Hz, 1 H) 8.13 (dd, $J=8.1, 1.0$ Hz, 1 H) 8.45 (s, 1 H) 10.35 (s, 1 H)
28	2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethoxyphenyl)-acetamide	380.3	381.1	(400 MHz, DMSO-d6) □ ppm 5.42 (s, 2 H) 7.05 (m, 1 H) 7.43 (m, 3 H) 7.66 (s, 1 H) 8.03 (d, $J=8.1$ Hz, 1 H) 8.15 (m, 1 H) 8.44 (s, 1 H) 10.71 (s, 1 H)
29	2-(7-Nitro-1H-	388.4	389.2	(400 MHz, DMSO-d6) □ ppm



	<b>benzoimidazol-1-yl)-N-(3-phenoxy-phenyl)-acetamide</b>			5.36 (s, 1 H) 6.71 (m, 1 H) 7.02 (m, 2 H) 7.13 (t, $J=7.3$ Hz, 1 H) 7.21 (t, $J=2.0$ Hz, 1 H) 7.28 (m, 2 H) 7.39 (m, 3 H) 8.01 (d, $J=7.6$ Hz, 1 H) 8.12 (dd, $J=8.1, 1.0$ Hz, 1 H) 8.42 (s, 1 H) 10.47 (s, 1 H)
30	<b>N-(4-Butyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	352.4	353.2	(400 MHz, DMSO-d6) □ ppm 0.87 (t, $J=7.3$ Hz, 3 H) 1.27 (m, 2 H) 1.50 (m, 2 H) 2.52 (m, 2 H) 5.37 (s, 2 H) 7.10 (d, $J=8.6$ Hz, 2 H) 7.41 (m, 3 H) 8.01 (d, $J=7.6$ Hz, 1 H) 8.13 (dd, $J=8.1, 1.01$ Hz, 1 H) 8.45 (s, 1 H) 10.29 (s, 1 H)
31	<b>N-(2-Fluoro-4-iodo-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	440.2	441.0	(400 MHz, DMSO-d6) □ ppm 5.46 (s, 2 H) 7.41 (t, $J=8.1$ Hz, 1 H) 7.49 (m, 1 H) 7.59 (t, $J=8.3$ Hz, 1 H) 7.70 (dd, $J=10.1, 2.0$ Hz, 1 H) 8.02 (dd, $J=8.1, 1.0$ Hz, 1 H) 8.13 (dd, $J=8.1, 1.0$ Hz, 1 H) 8.45 (s, 1 H) 10.35 (s, 1 H)
32	<b>2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(2-trifluoromethyl-benzyl)-acetamide</b>	378.3	379.2	(400 MHz, DMSO-d6) □ ppm 4.44 (d, $J=5.6$ Hz, 2 H) 5.32 (s, 2 H) 7.40 (t, $J=8.1$ Hz, 1 H) 7.48 (d, $J=7.6$ Hz, 1 H) 7.55 (d, $J=8.1$ Hz, 1 H) 7.68 (m, 2 H) 8.00 (d, $J=8.1$ Hz, 1 H) 8.11 (dd, $J=8.1, 1.0$ Hz, 1 H) 8.44 (s, 1 H) 8.86 (t, $J=5.8$ Hz,

				1 H)
33	<b><i>N</i>-(4-Methoxyphenyl)-2-(7-nitro-1<i>H</i>-benzimidazol-1-yl)acetamide</b>	326.3	325	(400 MHz, DMSO-D6) $\delta$ ppm 3.71 (s, 3H), 5.37 (s, 2 H), 6.88 (d, $J = 9.1$ Hz, 2 H), 7.44-7.40 (m, 3 H), 8.02 (d, $J = 7.8$ Hz, 1 H), 8.14 (d, $J = 7.8$ Hz, 1 H), 8.45 (s, 1 H), 10.24 (s, 1 H)
34	<b>2-(7-Nitro-1<i>H</i>-benzimidazol-1-yl)-<i>N</i>-[2-(trifluoromethoxy)phenyl]acetamide</b>	380.3	381	(400 MHz, DMSO-D6) $\delta$ ppm 5.49 (s, 2 H), 7.27-7.23 (m, 1 H), 7.37-7.33 (m, 1 H), 7.45-7.41 (m, 2 H), 7.80 (dd, $J = 8.1, 1.5$ Hz, 1 H), 8.03 (dd, $J = 8.1, 0.8$ Hz, 1 H), 8.14 (dd, $J = 8.0, 0.9$ Hz, 1 H), 8.50 (s, 1 H), 10.25 (s, 1 H)
35	<b>2-(7-Nitro-1<i>H</i>-benzimidazol-1-yl)-<i>N</i>-(2-phenoxyphenyl)acetamide</b>	388.4	389	(400 MHz, DMSO-D6) $\delta$ ppm 5.45 (s, 2 H), 6.87-6.85 (m, 1 H), 7.09-7.04 (m, 4 H), 7.18 (t, $J = 7.4$ Hz, 1 H), 7.44-7.40 (m, 3 H), 7.90-7.87 (m, 1 H), 8.02 (d, $J = 7.3$ Hz, 1 H), 8.13 (dd, $J = 8.0, 0.9$ Hz, 1 H), 8.45 (s, 1 H), 10.07 (s, 1 H)
36	<b><i>N</i>-(4-Bromo-2-fluorophenyl)-2-(7-nitro-1<i>H</i>-benzimidazol-1-yl)acetamide</b>	393.2	391	(400 MHz, DMSO-D6) $\delta$ ppm 5.48 (s, 2 H), 7.37 (d, $J = 8.8$ Hz, 1 H), 7.43 (t, $J = 8.1$ Hz, 1 H), 7.63 (dd, $J = 10.5, 2.2$ Hz, 1 H), 7.75 (t, $J = 8.7$ Hz, 1 H), 8.03 (d, $J = 7.6$ Hz, 1 H), 8.14 (dd, $J = 8.1, 0.8$ Hz, 1 H), 8.46

				(s, 1 H), 10.39 (s, 1 H)
37	<i>N</i> -[3-(Methylsulfonyl)phenyl]-2-(7-nitro-1 <i>H</i> -benzimidazol-1-yl)acetamide	374.4	373	(400 MHz, DMSO-D6) $\delta$ ppm 3.18 (s, 3 H), 5.45 (s, 2 H), 7.44 (t, $J = 8.1$ Hz, 1 H), 7.64- 7.59 (m, 2 H), 7.83-7.80 (m, 1 H), 8.05 (dd, $J = 8.1, 1.0$ Hz, 1 H), 8.17-8.15 (m, 2 H), 8.47 (s, 1 H), 10.85 (s, 1 H)
38	<i>N</i> -[4-(Methylsulfonyl)phenyl]-2-(7-nitro-1 <i>H</i> -benzimidazol-1-yl)acetamide	374.4	373	(400 MHz, DMSO-D6) $\delta$ ppm 3.16 (s, 3 H), 5.46 (s, 2 H), 7.44 (t, $J = 8.1$ Hz, 1 H), 7.77 (d, $J = 8.8$ Hz, 2 H), 7.87 (d, $J$ $= 8.8$ Hz, 2 H), 8.04 (d, $J = 7.3$ Hz, 1 H), 8.16 (dd, $J = 8.1, 1.0$ Hz, 1 H), 8.46 (s, 1 H), 10.90 (s, 1 H)
39	2-(7-Nitro-1 <i>H</i> -benzimidazol-1-yl)- <i>N</i> -[2-(trifluoromethoxy)phenyl]acetamide	324.3	323	(400 MHz, DMSO-D6) $\delta$ ppm 2.21 (s, 6 H), 5.38 (s, 2 H), 6.71 (s, 1 H), 7.13 (s, 2 H), 7.43 (t, $J = 8.1$ Hz, 1 H), 8.03 (dd, $J = 8.1, 0.8$ Hz, 1 H), 8.14 (dd, $J = 7.8, 1.0$ Hz, 1 H), 8.46 (s, 1 H), 10.24 (s, 1 H)
40	2-(7-Nitro-1 <i>H</i> -benzimidazol-1-yl)- <i>N</i> -[4-(trifluoromethyl)benzyl]acetamide	378.3	377	(400 MHz, DMSO-D6) $\delta$ ppm 4.37 (d, $J = 5.8$ Hz, 2 H), 5.29 (s, 2 H), 7.41 (t, $J = 8.0$ Hz, 1 H), 7.48 (d, $J = 7.8$ Hz, 2 H), 7.68 (d, $J = 8.1$ Hz, 2 H), 8.01 (d, $J = 8.1$ Hz, 1 H), 8.12 (d, $J$ $= 8.1$ Hz, 1 H), 8.43 (s, 1 H), 8.87 (t, $J = 5.7$ Hz, 1 H)

41	<i>N</i> -(4- <i>tert</i> -Butyl-benzyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	366.4	367	(400 MHz, CD <sub>3</sub> OD) □ ppm 1.30 (s, 9 H), 4.33 (s, 2 H), 5.33 (s, 2 H), 7.21 (d, <i>J</i> =8.34 Hz, 2 H), 7.35 (d, <i>J</i> =8.34 Hz, 2 H), 7.44 (t, <i>J</i> =8.08 Hz, 1 H), 8.04-8.09 (m, 2 H), 8.31 (s, 1 H)
42	<i>N</i> -Indan-5-yl-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	336.4	337	(400 MHz, CD <sub>3</sub> OD) □ ppm 2.00 - 2.10 (m, 2 H), 2.80-2.88 (m, 4 H), 5.43 (s, 2 H), 7.10 - 7.20 (m, 2 H), 7.35 (s, 1 H), 7.44 (t, <i>J</i> =8.08 Hz, 1 H), 8.05-8.10 (m, 2 H), 8.35 (s, 1 H)
43	2-(7-Nitro-1H-benzoimidazol-1-yl)- <i>N</i> -(4-trifluoromethoxy-benzyl)-acetamide	394.3	395	(400 MHz, CD <sub>3</sub> OD) □ ppm 4.39 (s, 2 H), 5.35 (s, 2 H), 7.21 (d, <i>J</i> =7.83 Hz, 2 H), 7.39 (d, <i>J</i> =8.59 Hz, 2 H), 7.44 (t, <i>J</i> =8.08 Hz, 1 H), 8.04-8.09 (m, 2 H), 8.32 (s, 1 H)
44	<i>N</i> -(4-Isopropyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	338.4	339	(400 MHz, CD <sub>3</sub> OD) □ ppm 1.21 (d, <i>J</i> =6.82 Hz, 6 H), 2.80 - 2.91 (m, <i>J</i> =6.86 Hz, 1 H), 5.44 (s, 2 H), 7.16 (d, <i>J</i> =8.59 Hz, 2 H), 7.38 (d, <i>J</i> =8.59 Hz, 2 H), 7.44 (t, <i>J</i> =8.08 Hz, 1 H), 8.08 (d, <i>J</i> =8.08 Hz, 2 H), 8.35 (s, 1 H)
45	<i>N</i> -(3,4-Dimethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide	324.3	325	(400 MHz, CD <sub>3</sub> OD) □ ppm 2.20 (s, 3H), 2.22 (s, 3 H), 5.49 (s, 2 H), 7.04 (d, <i>J</i> =8.34 Hz, 1 H), 7.19 (d, <i>J</i> =8.08 Hz,

				1 H), 7.25 (s, 1 H), 7.56 (t, $J=8.08$ Hz, 1 H), 8.10-8.19 (m, 2 H), 8.73 (s, 1 H)
46	<b><i>N</i>-Benzo[1,3]dioxol-5-yl-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	340.3	341	(400 MHz, CD <sub>3</sub> OD) □ ppm 5.42 (s, 2 H), 5.91 (s, 2 H), 6.74 (d, $J=8.34$ Hz, 1 H), 6.85 (dd, $J=8.34$ , 2.02 Hz, 1 H), 7.09 (d, $J=2.02$ Hz, 1 H), 7.45 (t, $J=8.08$ Hz, 1 H), 8.08 (d, $J=8.08$ , 2 H), 8.34 (s, 1 H)
47	<b><i>N</i>-(3-Bromo-4-trifluoromethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	459.2	460	(400 MHz, CD <sub>3</sub> OD) □ ppm 5.46 (s, 2 H), 7.33-37 (m, 1 H), 7.46 (t, $J=8.08$ Hz, 1 H), 7.55 (dd, $J=9.09$ , 2.53 Hz, 1 H), 7.97 (d, $J=2.53$ Hz, 1 H), 8.07-8.11 (m, 2 H), 8.35 (s, 1 H),
48	<b><i>N</i>-(3-Fluoro-2-methoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide</b>	344.3	345	(400 MHz, CD <sub>3</sub> OD) □ ppm 3.96 (d, $J=1.52$ Hz, 3 H), 5.55 (s, 2 H), 6.91 - 7.01 (m, 2 H), 7.45 (t, $J=8.08$ Hz, 1 H), 7.66 (d, $J=8.34$ Hz, 1 H), 8.09 (d, $J=8.08$ Hz, 2 H), 8.37 (s, 1 H)
49	<b><i>N</i>-(3,5-Dimethoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)propanamide</b>	370.4	371.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 1.96 (d, 3 H) 3.73 (s, 6 H) 5.57 (q, $J=7.2$ Hz, 1 H) 6.25 (t, $J=2.3$ Hz, 1 H) 6.75 (d, $J=2.0$ Hz, 2 H) 7.39 (t, $J=8.1$ Hz, 1 H) 7.96 (m, 1 H) 8.07 (dd, $J=8.1$ , 1.0 Hz, 1 H) 8.40 (s, 1 H) 8.57 (s, 1 H)

50	<b>2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-ethoxyphenyl)propanamide</b>	354.4	355.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 1.33 (t, <i>J</i> =6.8 Hz, 3 H) 1.96 (d, <i>J</i> =7.1 Hz, 3 H) 3.99 (q, <i>J</i> =7.1 Hz, 2 H) 5.58 (q, <i>J</i> =7.2 Hz, 1 H) 6.65 (m, 1 H) 7.03 (dd, <i>J</i> =8.1, 1.5 Hz, 1 H) 7.19 (m, 2 H) 7.38 (t, <i>J</i> =8.1 Hz, 1 H) 7.95 (dd, <i>J</i> =8.1, 1.0 Hz, 1 H) 8.07 (dd, <i>J</i> =8.1, 1.0 Hz, 1 H) 8.41 (s, 1 H) 8.61 (s, 1 H)
51	<b>2-(7-Nitro-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]propanamide</b>	378.3	379.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 1.98 (d, <i>J</i> =7.6 Hz, 3 H) 5.63 (q, <i>J</i> =7.2 Hz, 1 H) 7.40 (m, <i>J</i> =7.92, 7.92, 7.92 Hz, 2 H) 7.51 (t, <i>J</i> =8.1 Hz, 1 H) 7.71 (d, <i>J</i> =8.1 Hz, 1 H) 7.96 (m, 2 H) 8.08 (dd, <i>J</i> =8.1, 1.0 Hz, 1 H) 8.42 (s, 1 H) 8.89 (s, 1 H)
52	<b>2-(7-Bromo-1H-benzoimidazol-1-yl)-N-(3,5-dimethoxyphenyl)acetamide</b>	390.2	390.0	(400 MHz, DMSO-D <sub>6</sub> ) □ ppm 3.68 (s, 6 H) 5.38 (s, 2 H) 6.22 (t, <i>J</i> =2.3 Hz, 1 H) 6.81 (d, <i>J</i> =2.0 Hz, 2 H) 7.14 (t, <i>J</i> =8.1 Hz, 1 H) 7.41 (d, <i>J</i> =7.6 Hz, 1 H) 7.69 (d, <i>J</i> =7.6 Hz, 1 H) 8.26 (s, 1 H) 10.40 (s, 1 H)
53	<b>2-(7-bromo-1H-benzoimidazol-1-yl)-N-(3-methoxyphenyl)acetamide</b>	360.2	360.0	(400 MHz, DMSO-D <sub>6</sub> ) □ ppm 5.44 (m, 2 H) 7.15 (m, 1 H) 7.42 (m, 2 H) 7.57 (m, 1 H) 7.70 (dd, <i>J</i> =8.1, 0.9 Hz, 1 H) 7.75 (m, <i>J</i> =8.6, 1.2 Hz, 1 H) 8.04 (s, 1 H) 8.27 (m, 1 H)

				10.81 (s, 1 H)
54	2-(7-bromo-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide	398.2	398.0	(400 MHz, DMSO-D6) □ ppm 3.69 (s, 3 H) 5.40 (s, 2 H) 6.64 (ddd, $J=8.3, 2.5, 0.9$ Hz, 1 H) 7.08 (ddd, $J=8.1, 1.9, 0.8$ Hz, 1 H) 7.14 (m, 1 H) 7.21 (t, $J=8.1$ Hz, 1 H) 7.26 (m, 1 H) 7.41 (dd, $J=7.7, 0.7$ Hz, 1 H) 7.69 (dd, $J=8.0, 1.0$ Hz, 1 H) 8.27 (s, 1 H) 10.43 (s, 1 H)
55	2-(7-Chloro-1H-benzoimidazol-1-yl)-N-(3,5-dimethoxy-phenyl)-acetamide	345.8	346.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 3.73 (s, 6H), 5.29 (s, 2H), 6.26 (t, $J=2.2$ Hz, 1H), 6.78 (d, $J=2.1$ Hz, 2H), 7.19 – 7.27 (m, 2H), 7.66 (dd, $J=1.2, 7.6$ Hz, 1H), 7.97 (s, 1H), 8.64 (br.s, 1H)
56	2-(7-Chloro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethyl-phenyl)-acetamide	353.7	354.0	(400 MHz, CD <sub>3</sub> CN) □ ppm 5.42 (s, 2H), 7.15-7.30 (m, 2H), 7.41 (d, $J=7.9$ Hz, 1 H), 7.56 (t, $J=8.1$ Hz, 1 H), 7.73 (d, $J=8.1$ Hz, 1H), 7.80 (d, $J=7.9$ Hz, 1H), 7.98 (s, 1H), 8.02 (s, 1 H) 8.92 (s, 1 H)
57	2-(7-Chloro-1H-benzoimidazol-1-yl)-N-p-tolyl-acetamide	299.8	300.1	(400 MHz, CD <sub>3</sub> CN) □ ppm 2.27 (s, 3H), 5.31 (s, 2H), 7.12 (d, $J=8.2$ Hz, 2 H), 7.19 – 7.27 (m, 2H), 7.46 (d, $J=8.2$ Hz, 2H), 7.66 (dd, $J=1.2, 7.6$ Hz, 1H), 7.97 (s, 1H), 8.64 (br.s, 1H)

58	<b>2-(7-Methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)acetamide</b>	279.3	278	(400 MHz, DMSO-D6) $\delta$ ppm 2.25 (s, 3 H), 2.55 (s, 3 H), 5.29 (s, 2 H), 6.95 (d, $J = 7.3$ Hz, 1 H), 7.07 (t, $J = 7.7$ Hz, 1 H), 7.12 (d, $J = 8.3$ Hz, 2 H), 7.45-7.49 (m, 3 H), 8.11 (s, 1 H), 10.34 (s, 1 H)
59	<b>N-(3,5-Dimethoxyphenyl)-2-(7-methyl-1H-benzimidazol-1-yl)acetamide</b>	325.4	326	(400 MHz, DMSO-D6) $\delta$ ppm 2.54 (s, 3 H), 3.70 (s, 6 H), 5.29 (s, 2 H), 6.24 (t, $J = 2.0$ Hz, 1 H), 6.83 (d, $J = 2.0$ Hz, 2 H), 6.95 (d, $J = 7.3$ Hz, 1 H), 7.07 (t, $J = 7.6$ Hz, 1 H), 7.48 (d, $J = 8.1$ Hz, 1 H), 8.11 (s, 1 H), 10.42 (s, 1 H)
60	<b>2-(7-Methyl-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide</b>	333.3	334	(400 MHz, DMSO-D6) $\delta$ ppm 2.55 (s, 3 H), 5.36 (s, 2 H), 6.96 (d, $J = 7.3$ Hz, 1 H), 7.08 (t, $J = 7.7$ Hz, 1 H), 7.44 (d, $J$ $= 7.8$ Hz, 1 H), 7.49 (d, $J = 8.1$ Hz, 1 H), 7.59 (t, $J = 8.1$ Hz, 1 H), 7.79 (d, $J = 8.1$ Hz, 1 H), 8.07 (s, 1 H), 8.13 (s, 1 H), 10.81 (s, 1 H)
61	<b>3-[(3,4-Dimethylphenylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester</b>	337.4	338	(400 MHz, CD <sub>3</sub> OD) $\square$ ppm 2.19 (s, 3H), 2.21 (s, 3 H), 3.81 (s, 3 H), 5.48 (s, 2 H), 7.03 (d, $J=8.01$ Hz, 1 H), 7.22 (dd, $J=8.10, 2.25$ Hz, 1 H), 7.26 (d, $J=1.76$ Hz, 1 H), 7.34 (t, $J=7.81$ Hz, 1 H), 7.86 (dd,



				$J=7.62, 1.17 \text{ Hz}, 1 \text{ H}), 7.91$ (dd, $J=8.01, 1.17 \text{ Hz}, 1 \text{ H}),$ 8.22 (s, 1 H)
62	3-(Indan-5-ylcarbamoylmethyl)-3H-benzoimidazole-4-carboxylic acid methyl ester	349.4	350	(400 MHz, $\text{CD}_3\text{OD}$ ) $\square$ ppm 2.00 - 2.08 (m, $J=7.37 \text{ Hz}, 2$ H), 2.80 - 2.87 (m, 4 H), 5.48 (s, 2 H), 3.81 (s, 3 H), 7.11 (d, $J=8.00, 1 \text{ H}), 7.20$ (dd, $J=8.20, 1.95 \text{ Hz}, 1 \text{ H}), 7.34$ (t, $J=7.91 \text{ Hz}, 1 \text{ H}), 7.38$ (s, 1 H), 7.86 (dd, $J=7.71, 1.07 \text{ Hz}, 1$ H), 7.91 (dd, $J=8.10, 1.07 \text{ Hz},$ 1 H), 8.22 (s, 1 H)
63	3-[(4- <i>tert</i> -Butylbenzylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester	379.5	380	(400 MHz, $\text{CD}_3\text{OD}$ ) $\square$ ppm 1.29 (s, 9 H), 4.31 (s, 2 H), 3.75 (s, 3 H), 5.37 (s, 2 H), 7.21 (d, $J=8.59 \text{ Hz}, 2 \text{ H}), 7.30$ - 7.36 (m, 3 H), 7.84-7.92 (m, 2 H), 8.19 (s, 1 H)
64	3-[(3-Methoxy-5-trifluoromethylphenylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester	407.4	408	(400 MHz, $\text{CD}_3\text{OD}$ ) $\square$ ppm 3.81 (s, 3H), 3.81 (s, 3H), 5.53 (s, 2 H), 6.90 (s, 1 H), 7.36 (t, $J=7.91 \text{ Hz}, 1 \text{ H}), 7.47$ (s, 1 H), 7.45 (t, $J=1.95 \text{ Hz}, 1\text{H}), 7.87$ - 7.95 (m, 2 H), 8.23 (s, 1 H)
65	3-[(3,5-Dimethoxyphenylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester	369.4		(400 MHz, $\text{DMSO}-d_6$ ) $\square$ ppm 3.68 (s, 6H), 3.74 (s, 3H), 5.39 (s, 2H), 6.21 (t, $J=2.0 \text{ Hz}, 1\text{H}),$ 6.77 (d, $J=2.0 \text{ Hz}, 2\text{H}), 7.30$ (t, $J=7.8 \text{ Hz}, 1\text{H}), 7.72$ (d, $J=7.6$

				Hz, 1H), 7.93 (dd, $J=1.0$ , 8.1 Hz, 1H), 8.29 (s, 1H), 10.28 (s, 1H)
66	<i>N</i> -(3,5-Dimethoxyphenyl)-2-[7-[(dimethylamino)sulfonyl]-1 <i>H</i> -benzimidazol-1-yl]acetamide	418.5	417	(400 MHz, CDCl <sub>3</sub> ) $\delta$ ppm 2.89 (s, 6 H), 3.74 (s, 6 H), 5.42 (s, 2 H), 6.23 (s, 1 H), 6.72 (d, $J = 2$ Hz, 2 H), 7.39 (t, $J = 8.0$ Hz, 1 H), 7.70 (d, $J = 7.6$ Hz, 1 H), 8.05 (broad s, 1 H), 8.09 (d, $J = 7.8$ Hz, 1 H), 8.17 (s, 1 H)
67	2-[7-[(Dimethylamino)sulfonyl]-1 <i>H</i> -benzimidazol-1-yl]- <i>N</i> -[3-(trifluoromethyl)phenyl]acetamide	426.4	427	(400 MHz, DMSO-D <sub>6</sub> ) $\delta$ ppm 2.69 (s, 6 H), 5.59 (s, 2 H), 7.45-7.40 (m, 2 H), 7.57 (t, $J = 8.0$ Hz, 1 H), 7.73-7.69 (m, 2 H), 8.08-8.05 (m, 2 H), 8.37 (s, 1 H), 10.70 (s, 1 H)
68	<i>N</i> -(3,5-Dimethoxyphenyl)-2-[7-(propylsulfonyl)-1 <i>H</i> -benzimidazol-1-yl]acetamide	417.5	416	(400 MHz, DMSO-D <sub>6</sub> ) $\delta$ ppm 0.77 (t, $J = 7.4$ Hz, 3 H), 1.62-1.52 (m, 2 H), 3.29-3.24 (m, 2 H), 3.69 (s, 6 H), 5.60 (s, 2 H), 6.23 (t, $J = 2.2$ Hz, 1 H), 6.82 (d, $J = 2.3$ Hz, 2 H), 7.47 (t, $J = 7.8$ Hz, 1 H), 7.82 (dd, $J = 7.8$ , 0.8 Hz, 1 H), 8.11 (dd, $J = 8.1$ , 1.0 Hz, 1 H), 8.41 (s, 1 H), 10.49 (s, 1 H)
69	2-[7-(Propylsulfonyl)-1 <i>H</i> -benzimidazol-1-yl]- <i>N</i> -[3-(trifluoromethyl)phenyl]acetamide	425.4	426	(400 MHz, DMSO-D <sub>6</sub> ) $\delta$ ppm 0.74 (t, $J = 7.4$ Hz, 3 H), 1.60-1.50 (m, 2 H), 3.29-3.24 (m, 2 H), 5.64 (s, 2 H), 7.43 (d, $J =$

				7.8 Hz, 1 H), 7.48 (t, $J = 7.8$ Hz, 1 H), 7.58 (t, $J = 8.0$ Hz, 1 H), 7.73 (d, $J = 8.6$ Hz, 1 H), 7.82 (d, $J = 7.8$ Hz, 1 H), 8.09 (s, 1 H), 8.12 (dd, $J = 8.1, 1.0$ Hz, 1 H), 8.42 (s, 1 H), 10.88 (s, 1 H)
70	<b><i>N</i>-(3,5-Dimethoxyphenyl)-2-[7-(trifluoromethyl)-1<i>H</i>-benzimidazol-1-yl]acetamide</b>	379.3	378	(400 MHz, DMSO- $D_6$ ) $\delta$ ppm 3.69 (s, 6 H), 5.28 (s, 2 H), 6.22 (t, $J = 2.3$ Hz, 1 H), 6.78 (d, $J = 2.3$ Hz, 2 H), 7.41 (t, $J = 7.8$ Hz, 1 H), 7.65 (d, $J = 7.6$ Hz, 1 H), 8.04 (d, $J = 8.1$ Hz, 1 H), 8.37 (s, 1 H), 10.41 (s, 1H)

## Example 71

**2-(7-amino-1*H*-benzimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide**

To a solution of 2-(7-nitro-1*H*-benzimidazol-1-yl)-*N*-[3-

- 5 (trifluoromethyl)phenyl]acetamide, described above, (0.4 g, 1.1 mmol) in methanol (15 mL) 10% Pd/C (60 mg) was added. The mixture was hydrogenated at atmospheric pressure until the consumption of hydrogen ceased (1 h). The catalyst was removed by filtration through Celite, and the resulting clear solution was concentrated to dryness to yield the title compound, 0.36 g (99%). MS (ESI)  $m/z$ : 335.07  $[M+H]^+$ .  $^1H$  NMR (400 MHz, DMSO-  
 10  $D_6$ )  $\delta$  ppm 4.91 (s, 2 H) 5.33 (s, 2 H) 6.50 (m, 1 H) 6.89 (t,  $J = 7.6$  Hz, 1 H) 6.97 (m, 1 H) 7.41 (d,  $J = 7.6$  Hz, 1 H) 7.56 (t,  $J = 7.8$  Hz, 1 H) 7.77 (m, 1 H) 7.99 (s, 1 H) 8.07 (s, 1 H) 10.84 (s, 1 H).

## Example 72

**2-[7-(acetylamino)-1*H*-benzimidazol-1-yl]-*N*-[3-(trifluoromethyl)phenyl]acetamide**

To a chilled (0 °C) solution of 2-(7-amino-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide (example 71) (15 mg, 45  $\mu$ mol) and triethylamine (13  $\mu$ L, 90  $\mu$ mol) in dry dichloromethane (0.5 mL) acetyl chloride (3.7  $\mu$ L, 50  $\mu$ mol) was added and the reaction mixture was allowed to warm up to ambient temperature. After 30 min methanol (1 mL) was added and the volatiles were removed under reduced pressure. The title compound was Purification on preparative HPLC yielded the title compound, 11 mg (65%).

MS (ESI) *m/z*: 377.13 [M+H]. <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>)  $\delta$  ppm 1.98 (s, 3 H) 5.20 (s, 2 H) 6.90 (m, 1 H) 7.15 (m, 1 H) 7.41 (m, 1 H) 7.56 (m, 2 H) 7.70 (m, 1 H) 8.07 (s, 1 H) 8.12 (s, 1 H) 9.83 (s, 1 H) 10.73 (s, 1 H).

#### Example 73

##### 2-[7-[(methylsulfonyl)amino]-1*H*-benzoimidazol-1-yl]-*N*-[3-(trifluoromethyl)phenyl]acetamide

To a chilled (0 °C) solution of 2-(7-amino-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide (example 71) (15 mg, 45  $\mu$ mol) and triethylamine (13  $\mu$ L, 90  $\mu$ mol) in dry dichloromethane (0.5 mL) methanesulfonyl chloride (8  $\mu$ L, 100  $\mu$ mol) was added and the reaction mixture was allowed to warm up to ambient temperature. After 30 min methanol (1 mL) was added, and the volatiles were removed under reduced pressure. The residue was dissolved in methanol (2 mL) and aqueous benzyltrimethylammonium hydroxide (40%, 200  $\mu$ L) was added, the mixture was kept at room temperature for 1 h, then partitioned between ethyl acetate and phosphate buffer (pH 7). The organic phase was dried over magnesium sulfate and concentrated. Purification on preparative HPLC yielded the title compound, 13 mg (71%). MS (ESI) *m/z*: 413.03 [M+H]. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN)  $\delta$  ppm 3.02 (s, 3 H) 5.37 (s, 2 H) 7.20 (dd, *J*=7.6, 1.0 Hz, 1 H) 7.27 (t, *J*=7.8 Hz, 1 H) 7.41 (d, *J*=8.1 Hz, 1 H) 7.51 (t, *J*=7.8 Hz, 1 H) 7.69 (dd, *J*=8.1, 1.0 Hz, 1 H) 7.73 (d, *J*=8.6 Hz, 1 H) 7.96 (s, 1 H) 7.98 (s, 1 H) 9.13 (s, 1 H).

#### Example 74

##### 2-[7-(dimethylamino)-1*H*-benzoimidazol-1-yl]-*N*-[3-(trifluoromethyl)phenyl]acetamide

To a solution of 2-(7-amino-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide (example 71) (22 mg, 66  $\mu$ mol) and 37% aqueous formaldehyde (100  $\mu$ L, 1.2 mmol) in ethanol (1 mL), acetic acid (60  $\mu$ L) and sodium cyanoborohydride (30 mg, 0.5 mmol) were added. After 30 min the volatiles were removed under reduced pressure, and the residue was purified on preparative HPLC to yield the title compound, 8.5 mg (36%). MS (ESI) *m/z*: 363.18 [M+H]. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN)  $\delta$  ppm 2.66 (s, 6 H) 5.25 (s, 2 H) 7.13 (d, *J*=8.1 Hz, 1 H) 7.19 (t, *J*=7.8 Hz, 1 H) 7.40 (d, *J*=8.1 Hz, 1 H) 7.45 (m, 1 H) 7.50 (t, *J*=8.1 Hz, 1 H) 7.75 (d, *J*=8.1 Hz, 1 H) 7.92 (s, 1 H) 7.97 (s, 1 H) 8.93 (s, 1 H).

#### Example 75

##### 2-[7-(Isopropylamino)-1*H*-benzoimidazol-1-yl]-*N*-[3-(trifluoromethyl)phenyl]acetamide

The title compound was prepared in 15 mg (59%) yield according to the procedure described in example 74, using acetone (100  $\mu$ L) instead of formaldehyde. MS (ESI) *m/z*: 377.20 [M+H]. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 1.16 (d, *J*=6.1 Hz, 6 H) 3.59 (m, 1 H) 5.34 (s, 2 H) 6.70 (m, 1 H) 7.13 (m, 2 H) 7.40 (d, *J*=8.1 Hz, 1 H) 7.51 (t, *J*=8.1 Hz, 1 H) 7.79 (d, *J*=8.1 Hz, 1 H) 7.98 (s, 1 H) 7.99 (s, 1 H).

#### Example 76

##### 2-(7-Cyano-1*H*-benzoimidazol-1-yl)-*N*-(3,5-dimethoxyphenyl)acetamide

To a solution of 2-(7-bromo-1*H*-benzoimidazol-1-yl)-*N*-(3,5-dimethoxyphenyl)acetamide (example 52) (50 mg, 0.13 mmol) in dry DMF (0.64 mL) copper(I) cyanide (23 mg, 0.26 mmol) was added. The mixture was irradiated in a microwave oven at 200 °C for 60 min.

The reaction mixture was partitioned between ethyl acetate and water. The organic extract was concentrated and the residue was purified by preparative HPLC to yield the title compound, 20 mg (46%). MS (ESI) *m/z*: 337.2 [M+H]. <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>)  $\delta$  ppm 3.69 (s, 6 H) 5.39 (s, 2 H) 6.23 (t, *J*=2.3 Hz, 1 H) 6.80 (d, *J*=2.0 Hz, 2 H) 7.37 (t, *J*=7.8 Hz, 1 H) 7.74 (d, *J*=7.1 Hz, 1 H) 8.05 (dd, *J*=8.1, 1.0 Hz, 1 H) 8.40 (s, 1 H) 10.47 (s, 1 H).

#### Example 77

**2-(7-Cyano-1H-benzoimidazol-1-yl)-N-(3-methoxyphenyl)acetamide**

The title compound was prepared in 4.2 mg (23 %) yield from 2-(7-bromo-1H-benzoimidazol-1-yl)-N-(3-methoxyphenyl)acetamide (example 53) according to the procedure described in example 76. MS (ESI)  $m/z$ : 307.12 [M+H].  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\square$  ppm 3.75 (s, 3 H) 5.32 (s, 2 H) 6.69 (dd,  $J=8.3$ , 1.8 Hz, 1 H) 7.06 (dd,  $J=7.8$ , 1.3 Hz, 1 H) 7.24 (m, 2 H) 7.37 (t,  $J=7.8$  Hz, 1 H) 7.67 (dd,  $J=7.6$ , 1.0 Hz, 1 H) 8.02 (dd,  $J=8.1$ , 1.0 Hz, 1 H) 8.09 (s, 1 H) 8.70 (s, 1 H).

**Example 78****2-(7-Cyano-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide**

The title compound was prepared in 3.5 mg (18 %) yield from 2-(7-bromo-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide (example 54) according to the procedure described in example 76. MS (ESI)  $m/z$ : 345.05 [M+H].  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\square$  ppm 5.36 (s, 2 H) 7.38 (dd,  $J=8.2$ , 7.7 Hz, 1 H) 7.43 (m, 1 H) 7.53 (t,  $J=7.8$  Hz, 1 H) 7.68 (dd,  $J=7.6$ , 0.8 Hz, 1 H) 7.74 (m, 1 H) 7.96 (s, 1 H) 8.02 (dd,  $J=8.3$ , 1.0 Hz, 1 H) 8.11 (s, 1 H) 8.96 (s, 1 H).

**Example 79****2-[7-(1H-tetrazol-5-yl)-1H-benzoimidazol-1-yl]-N-(3,5-dimethoxyphenyl)acetamide**

To a suspension of 2-(7-cyano-1H-benzoimidazol-1-yl)-N-(3,5-dimethoxyphenyl)acetamide (example 76) (12 mg, 36  $\mu\text{mol}$ ) in water (0.2 mL) sodium azide (6.6 mg, 100  $\mu\text{mol}$ ) and zinc bromide (22.5 mg, 100  $\mu\text{mol}$ ) were added. The mixture was heated in a sealed vial at 105  $^\circ\text{C}$  under vigorous stirring for 24 h. After cooling the mixture was acidified to pH 4 with 2M HCl, and extracted with ethyl acetate. The extract was washed with water, brine, dried over sodium sulfate and concentrated. Purification by preparative HPLC yielded the title compound, 3.5 mg (26 %). MS (ESI)  $m/z$ : 380.1 [M+H].

**Pharmacology**

DRGs were dissected out from adult Sprague Dawley rats (100-300 gr), and placed on ice in L15 Leibovitz medium. The ganglia were enzyme treated with Collagenase 80U/ml+

Disperse 34 U/ml dissolved in DMEM +5% serum, overnight at 37 °C. The next day, cells were triturated with fire polished pasteur pipettes, and seeded in the center of 58 mm diameter Nunc cell dishes coated with Poly-D Lysine (1 mg/mL). The DRGs were cultured in a defined medium without foetal bovine serum, containing Dulbecco's MEM / NUT MIX F-12 (1:1) without L-glutamine but with pyridoxine, 6 mg/mL D(+)-Glucose, 100 µg/mL apo-transferrin, 1 mg/mL BSA, 20 µg/mL insulin, 2 mM L-glutamine, 50 IU/ mL Penicillin, 50 µg / mL Streptomycin and 0.01 µg/mL NGF-7S.

When the cells had grown for 2 days up to 4 weeks, the experiments were done. Cells were chosen based on size and presence of neurites. Small cells with long processes were used for recording (most likely to be C neurons, with native VR1 receptors).

The cells were recorded with conventional whole cell voltage clamp patch clamp, using the following solutions (calcium ion free):

The extracellular solution comprised (in mM): NaCl 137, KCl 5, MgCl<sub>2</sub> \* H<sub>2</sub>O 1.2, HEPES 10, Glucose 10, EGTA 5, Sucrose 50, pH to 7.4 with NaOH.

The intracellular solution comprised K-gluconate 140, NaCl 3, MgCl<sub>2</sub> \* H<sub>2</sub>O 1.2, HEPES 10, EGTA 1, pH to 7.2 with KOH. When the cells were penetrated with suction, a puff of capsaicin (500 nM) was used to determine if the cell expressed VR1 receptor. If not, a new cell was chosen. If yes, then the compounds were added in increasing doses before the capsaicin pulse (500 nM), to determine an IC<sub>50</sub> value.

#### List of abbreviations

VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
DRG	Dorsal Root Ganglion
BSA	Bovine Serum Albumin
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
EGTA	Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid
DMEM	Dulbeccos Modified Eagle's Medium

**Results**

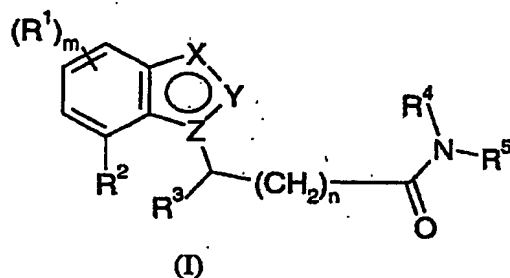
- 5 Typical  $IC_{50}$  values as measured in the assays described above are 10  $\mu$ M or less. In one aspect of the invention the  $IC_{50}$  is below 500 nM. In another aspect of the invention the  $IC_{50}$  is below 100 nM. In a further aspect of the invention the  $IC_{50}$  is below 10 nM.

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## CLAIMS

1. A compound having the formula I



5 wherein:

R<sup>1</sup> is H, NO<sub>2</sub>, NH<sub>2</sub>, halo, NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkylO, C<sub>1-6</sub>alkylOC<sub>0-6</sub>alkyl, R<sup>6</sup>OC<sub>1-6</sub>alkyl, R<sup>6</sup>CO, CO<sub>2</sub>R<sup>6</sup> or CONR<sup>6</sup>R<sup>7</sup>;

m is 0, 1, 2, 3 or 4;

10 R<sup>2</sup> is H, NO<sub>2</sub>, NH<sub>2</sub>, halo, NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkylO, C<sub>0-6</sub>alkylcyano, C<sub>1-6</sub>alkylOC<sub>0-6</sub>alkyl, R<sup>6</sup>OC<sub>1-6</sub>alkyl, R<sup>6</sup>CO, CO<sub>2</sub>R<sup>6</sup> or CONR<sup>6</sup>R<sup>7</sup>, R<sup>8</sup>SO<sub>2</sub>, arylC<sub>0-6</sub>alkyl, heteroarylC<sub>0-6</sub>alkyl, NR<sup>6</sup>R<sup>7</sup>, NCOR<sup>6</sup>, NHCOR<sup>6</sup> or NHSO<sub>2</sub>R<sup>6</sup>;

X, Y and Z are each independently C, CR<sup>6</sup>, N or NR<sup>6</sup>;

R<sup>3</sup> is H or C<sub>0-4</sub>alkyl;

15 n is 0, 1, 2, 3 or 4;

R<sup>4</sup> is H or C<sub>0-4</sub>alkyl;

R<sup>5</sup> is H, C<sub>1-10</sub>alkyl, C<sub>5-6</sub>aryl, C<sub>3-7</sub>cycloalkyl, C<sub>5-6</sub>heteroaryl, whereby any aryl or cycloalkyl may be fused with heteroaryl, C<sub>3-7</sub>cycloalkyl or C<sub>3-7</sub>heterocycloalkyl;

and R<sup>4</sup> and R<sup>5</sup> may be substituted with one or more A; and

20 A is H, OH, NO<sub>2</sub>, NH<sub>2</sub>, CO, O(CO), halo, C<sub>1-6</sub>alkyl, NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>alkylOC<sub>0-6</sub>alkyl, R<sup>6</sup>OC<sub>1-6</sub>alkyl, R<sup>6</sup>CO, CO<sub>2</sub>R<sup>6</sup> or CONR<sup>6</sup>R<sup>7</sup>;

R<sup>6</sup> and R<sup>7</sup> are each independently H or C<sub>1-6</sub>alkyl;

R<sup>8</sup> is NR<sub>6</sub>R<sub>7</sub> or C<sub>0-4</sub>alkyl

or salts, solvates or solvated salts thereof,

25 with the proviso the compound is not 2-Indol-1-yl-N-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide.

2. The compounds selected from the group consisting of

- N-(3-Fluoro-4-methoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(2-Fluoro-4-trifluoromethylphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Chloro-4-iodo-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
5 N-(3-Chloro-4-methoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Difluoromethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Methoxy-5-trifluoromethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,5-Difluoro-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethoxy-phenyl)-acetamide,  
10 N-(3-Methoxy-5-trifluoromethyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-acetamide,  
N-(4-tert-Butyl-phenyl)-2-(7-nitrobenzoimidazol-1-yl)-acetamide,  
N-[3-(1-Hydroxy-ethyl)-phenyl]-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(4-trifluoromethyl-phenyl)-acetamide,  
15 N-(3-Chloro-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-Hexyl-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,4-Difluoro-phenyl)-2-(7-nitrobenzoimidazol-1-yl)-acetamide,  
N-(4-Cyano-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
20 N-(2-Bromo-benzyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethyl-benzyl)-acetamid,  
N-(4-Methyl-pyridin-2-yl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Cyano-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,5-Dimethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
25 N-(3-Methoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3-Ethoxyphenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(3,4-Dimethoxy-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3,4,5-trimethoxy-phenyl)-acetamide,  
2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-trifluoromethoxyphenyl)-acetamide,  
30 2-(7-Nitro-1H-benzoimidazol-1-yl)-N-(3-phenoxy-phenyl)-acetamide,  
N-(4-Butyl-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,  
N-(2-Fluoro-4-iodo-phenyl)-2-(7-nitro-1H-benzoimidazol-1-yl)-acetamide,

- 2-(7-Nitro-1H-benzimidazol-1-yl)-N-(2-trifluoromethyl-benzyl)-acetamide,  
N-(4-Methoxyphenyl)-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[2-(trifluoromethoxy)phenyl]acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-(2-phenoxyphenyl)acetamide,  
5 N-(4-Bromo-2-fluorophenyl)-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
N-[3-(Methylsulfonyl)phenyl]-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
N-[4-(Methylsulfonyl)phenyl]-2-(7-nitro-1H-benzimidazol-1-yl)acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[2-(trifluoromethoxy)phenyl]acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-[4-(trifluoromethyl)benzyl]acetamide,  
10 N-(4-tert-Butyl-benzyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-Indan-5-yl-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-(4-trifluoromethoxy-benzyl)-acetamide,  
N-(4-Isopropyl-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-(3,4-Dimethyl-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
15 N-Benzo[1,3]dioxol-5-yl-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-(3-Bromo-4-trifluoromethoxy-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-(3-Fluoro-2-methoxy-phenyl)-2-(7-nitro-1H-benzimidazol-1-yl)-acetamide,  
N-(3,5-Dimethoxyphenyl)-2-(7-nitro-1H-benzimidazol-1-yl)propanamide,  
2-(7-Nitro-1H-benzimidazol-1-yl)-N-(3-ethoxyphenyl)propanamide,  
20 2-(7-Nitro-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]propanamide,  
2-(7-Bromo-1H-benzimidazol-1-yl)-N-(3,5-dimethoxyphenyl)acetamide,  
2-(7-bromo-1H-benzimidazol-1-yl)-N-(3-methoxyphenyl)acetamide,  
2-(7-bromo-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide,  
2-(7-Chloro-1H-benzimidazol-1-yl)-N-(3,5-dimethoxy-phenyl)-acetamide,  
25 2-(7-Chloro-1H-benzimidazol-1-yl)-N-(3-trifluoromethyl-phenyl)-acetamide,  
2-(7-Chloro-1H-benzimidazol-1-yl)-N-p-tolyl-acetamide,  
2-(7-Methyl-1H-benzimidazol-1-yl)-N-(4-methylphenyl)acetamide,  
N-(3,5-Dimethoxyphenyl)-2-(7-methyl-1H-benzimidazol-1-yl)acetamide,  
2-(7-Methyl-1H-benzimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide,  
30 3-[(3,4-Dimethyl-phenylcarbamoyl)-methyl]-3H-benzimidazole-4-carboxylic acid methyl  
ester,  
3-(Indan-5-ylcarbamoylmethyl)-3H-benzimidazole-4-carboxylic acid methyl ester,

3-[(4-tert-Butyl-benzylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester,

3-[(3-Methoxy-5-trifluoromethyl-phenylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester,

5 3-[(3,5-Dimethoxy-phenylcarbamoyl)-methyl]-3H-benzoimidazole-4-carboxylic acid methyl ester,

N-(3,5-Dimethoxyphenyl)-2-{7-[(dimethylamino)sulfonyl]-1H-benzimidazol-1-yl}acetamide,

2-{7-[(Dimethylamino)sulfonyl]-1H-benzimidazol-1-yl}-N-[3-(trifluoromethyl)phenyl]acetamide,

10 N-(3,5-Dimethoxyphenyl)-2-[7-(propylsulfonyl)-1H-benzimidazol-1-yl]acetamide,

2-[7-(Propylsulfonyl)-1H-benzimidazol-1-yl]-N-[3-(trifluoromethyl)phenyl]acetamide and

N-(3,5-Dimethoxyphenyl)-2-[7-(trifluoromethyl)-1H-benzimidazol-1-yl]acetamide, or salts, solvates or solvated salts thereof.

15

3. The compound according to any one of claims 1 to 2, for use in therapy.

4. Use of the compound according to any one of claims 1 to 2, in treatment of VR1 mediated disorders.

20

5. The use according to claim 3 for treatment of acute and chronic pain disorders.

6. The use according to claim 3 for treatment of acute and chronic inflammatory pain.

25

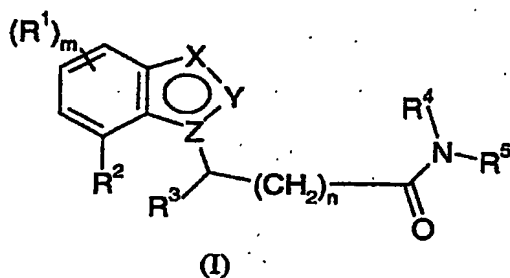
7. The use according to claim 3 for treatment of indications selected from the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatica, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

30

8. Use of the compound of formula I according to any one of claims 1 to 2, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.
- 5 9. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain, comprising administering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 2.
- 10 10. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 2, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.
- 15 11. The pharmaceutical formulation according to claim 10, for use in the treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

## ABSTRACT

The present invention relates to new compounds of formula I,



- 5 wherein  $R^1$  to  $R^5$  are as defined as in formula I, or salts, solvates or solvated salts thereof, processes for their preparation and to new intermediates used in the preparation thereof, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy.